Title:

Diffusion Tensor Imaging Studies of Attention-Deficit/Hyperactivity Disorder: Meta-analyses and reflections on head motion

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Abbreviated title: Meta-analyses of ADHD DTI studies

Authors:

Yuta Aoki1, Samuele Cortese1,2, F. Xavier Castellanos1,3

Affiliations:

1 Department of Child and Adolescent Psychiatry, NYU Langone Medical Center, New York, NY, USA

2 Academic Unit of Psychology, Developmental Brain-Behaviour Laboratory, Unit of Psychology, Clinical and Experimental Sciences (CNS and Psychiatry), University of Southampton, UK, and Solent NHS Trust, Southampton, UK

3 Nathan S. Kline Institute for Psychiatric Research, Orangeburg, NY, USA

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\*Corresponding Author:

Yuta Aoki, M.D., Ph.D.

The Child Study Center at NYU Langone Medical Center,

One Park Avenue, New York, NY 10016, USA

E-mail: yuta.aoki@nyumc.org

Phone number: +1 917 903 6972

**Abstract**

**Background:** Diffusion tensor imaging studies have shown atypical fractional anisotropy (FA) in individuals with attention-deficit/hyperactivity disorder (ADHD), albeit with conflicting results. We performed meta-analyses of whole-brain voxel-based analyses (WBVBA) and tract-based spatial statistics (TBSS) studies in ADHD, along with a qualitative review of TBSS studies addressing the issue of head motion, which may bias results.

**Methods:** We conducteda systematic literature search (last search on April 1st, 2016) to identify studies comparing FA values between individuals with ADHD and typically developing (TD) participants. Anisotropic algorithms were used to compute effect sizes and integrated WBVBA and TBSS studies, separately. TBSS datasets reporting no between-group motion differences were identified.

**Results:** Weidentified 14 WBVBA (ADHD n=314, TD n=278) and 13 TBSS datasets (ADHD n=557, TD n=568). WBVBA meta-analysis showed both significantly lower and higher FA values in individuals with ADHD; TBSS meta-analysis showed significantly lower FA in ADHD compared with TD in four clusters: two in the corpus callosum (isthmus and posterior midbody), one in right inferior fronto-occipital fasciculus, and one in left inferior longitudinal fasciculus. However, four out of six datasets confirming no group-differences in motion showed no significant between-group FA differences.

**Conclusions:** A growing DTI literature (total N=1717) and a plethora of apparent findings suggest atypical interhemispheric connection in ADHD. However, FA results in ADHD should be considered with caution, since many studies did not examine potential group differences in head motion, and most of the studies reporting no difference in motion showed no significant results. Future studies should address head motion as a priority and assure that groups do not differ in head motion.

(261/300 words)

**[Keywords]**

**ADD, ADHD, DTI, head motion, meta-analysis**

**Introduction**

Attention-deficit/hyperactivity disorder (ADHD) is characterized by age-inappropriate and impairing inattention and/or hyperactivity-impulsivity ([American Psychiatric, 2013](#_ENREF_2)). Despite its high prevalence and impact ([Thapar and Cooper, 2016](#_ENREF_55)), the pathophysiology of ADHD remains unclear, although abnormal brain connectivity has been proposed as a key substrate ([reviewed in Castellanos and Aoki, 2016](#_ENREF_9)). Structural connectivity can be probed using diffusion tensor imaging (DTI) to quantify Brownian motion of water molecules which is restricted in brain by microstructural components such as axons or myelin ([Taylor et al., 2004](#_ENREF_54)). Deviations from isotropic or spherical diffusion (termed anisotropic diffusion) indirectly reflect alterations in white matter microarchitecture. Fractional anisotropy (FA) is a commonly used DTI index which varies between 0 (maximally isotropic) and 1 (maximally anisotropic).

DTI indices such as FA can be analyzed in *a priori* selected regions-of-interest (ROI) or via whole-brain voxel-based methods. Although ROI methods are most sensitive to potential differences in the selected tracts, they provide no information about areas outside the ROI and are not amenable to meta-analysis. By contrast, exploratory voxel-based methods can detect abnormalities in tracts not considered in ROI studies. Analyses encompassing all voxels in the brain are referred to as *whole brain voxel-based analyses* (WBVBA). Although this approach is maximally inclusive, aligning individual white matter maps into a common standard white matter space is challenging due to difficulty in aligning FA images from multiple subjects ([Smith et al., 2006](#_ENREF_52)). An alternative approach, named *tract-based spatial statistics* (TBSS) ([Smith et al., 2006](#_ENREF_52)), minimizes potential misalignment problems. This is accomplished by first determining a mean FA “skeleton” and then mapping DTI data from each participant directly onto the skeleton for group comparisons ([Smith et al., 2007](#_ENREF_53)). Because the centers of the major tracts are easily definable, despite anatomic heterogeneity across individuals, TBSS has become the leading approach for group inferential testing of DTI data.

 DTI studies of ADHD have used both approaches. The body of research on DTI in ADHD has progressively increased over the last years, so that it is amenable to meta-analytic synthesis. The first meta-analysis of ADHD studies pooled seven WBVBA and two TBSS DTI studies, despite the difficulty of combining both approaches ([Van Ewijk et al., 2012](#_ENREF_57)). By contrast, a recent meta-analysis integrated 10 TBSS ADHD studies and excluded WBVBA approaches ([Chen et al., 2016](#_ENREF_12)). Both meta-analyses showed lower FA values in individuals with ADHD, while no regions with higher FA in individuals with ADHD were observed. The first meta-analysis ([Van Ewijk et al., 2012](#_ENREF_57)) suggested alteration of white matter organization in the fronto-striatal-cerebellar circuitry, while the second meta-analysis ([Chen et al., 2016](#_ENREF_12)) reported abnormalities in commissural fibers associated with cross-sectional age. However, neither meta-analysis separately conducted meta-analyses of WBVBA and TBSS nor considered the observation that head motion produces spurious DTI findings of decreased FA in groups with greater head motion ([Yendiki et al., 2014](#_ENREF_60)). Head motion is a particular concern in ADHD, which is characterized by hyperkinesis in both children and adults ([Garcia Murillo et al., 2015](#_ENREF_24)). Accordingly, we performed updated meta-analyses of both WBVBA and TBSS approaches, separately. Because of the concerns regarding head motion, we also provided a qualitative review on the potential influence of head motion on TBSS studies that compared head motion during the scan. Such an analysis was not possible for the WBVBA studies, which were largely conducted before the field became aware of head motion as a concern.

**Methods**

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement was followed for the systematic search ([Moher et al., 1999](#_ENREF_36)).

**Data sources**

Two authors (Y.A. and S.C.) independently searched the following electronic databases: PubMed, Ovid databases (Ovid MEDLINE®, EMBASE Classic+EMBASE, PsycINFO), Web of Knowledge (including Web of Science, Biological Abstracts, BIOSIS, Current Contents Connect, Data Citation Index, Derwet Innovations Index, FSTA, INspec, MEDLINE, and SciELO), and ERIC, without language and date restrictions. The last search was performed on April 1st, 2016. Supplemental Material A1 reports the search terms and syntax for each electronic database.

**Identification and selection of studies**

First, two authors (Y.A. and S.C.) independently screened titles and abstracts of all non-duplicated papers and agreed on a final list of studies that proceeded to full-text screening. Then, the two authors independently assessed eligibility of these studies for the meta-analysis. Reference lists of the identified studies were also screened to determine if any relevant studies had been missed during the database searches. Any discrepancy between the two authors was resolved by a third author (F.X.C.).

**Selection of study**

Studies were included in the meta-analysis if they:

1. were peer-reviewed, indicating methodological adequacy. This is in line with recent meta-analyses (e.g., [Daley et al., 2014](#_ENREF_20), [Cortese et al., 2015](#_ENREF_17)).
2. recruited individuals diagnosed with ADHD based on semi-structured interviews according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III and following editions) or International Classification of Diseases (ICD-9 or 10) and TD controls without psychiatric diagnoses. Datasets including individuals with a past but not current diagnosis of ADHD were not included in the present study, because it is unclear whether the neural correlates of individuals with ADHD in partial remission are similar to those with the full syndrome ([Cortese et al., 2012](#_ENREF_19)). One study ([Bode et al., 2015](#_ENREF_7)) and one dataset from one study ([Cortese et al., 2013](#_ENREF_18)) were excluded from analysis for this reason. In the Cortese et al. study, the dataset with a current ADHD diagnosis was included in the analysis ([Cortese et al., 2013](#_ENREF_18)).
3. compared FA values between individuals with ADHD and TD using either TBSS or WBVBA. Studies that reported only results of ROI analyses were excluded, because this violates the assumption underlying the meta-analytic procedure that, under the null hypothesis, all voxels will show the same difference between groups. We selected FA as the DTI parameter for the primary analysis, because it is the most often used in DTI studies, especially older ones.

**Data extraction**

When more than one statistical threshold was used in a study, we chose the most stringent threshold, similarly to previous work ([Schulze et al., 2016](#_ENREF_47)). Similar results were obtained when we adopted the most lenient threshold (results available upon request). Then, we extracted peak-coordinates and their effect sizes. In studies not providing exact effect sizes for peak-coordinates, the study threshold for significance was interpreted as the effect size, as in previous reports, (e.g., [Aoki and Inokuchi, 2016](#_ENREF_4), [Schulze et al., 2016](#_ENREF_47)). In cases where peak coordinates and/or effect sizes were not provided, we contacted the corresponding author(s) to obtain the missing data. For a secondary analysis, we also extracted peak-coordinates and the corresponding effect sizes of voxel-level group comparisons of mean diffusivity (MD) when available. P-values of peak coordinates were converted to t-values using the anisotropic effect size signed differential mapping (AES-SDM) utility (http://www.sdmproject.com/utilities/?show=Statistics). The FA and MD peak coordinates and their effect sizes are available upon request from the authors.

**Meta-analysis**

Similarly to previous meta-analyses ([Nakao et al., 2011](#_ENREF_38), [Nortje et al., 2013](#_ENREF_39), [Aoki et al., 2015](#_ENREF_3), [Wise et al., 2016](#_ENREF_59)), we used the AES-SDM software (www.sdmproject.com/software/) to analyze regional differences in FA and MD values between individuals with ADHD and TD controls. Meta-analyses of studies of WBVBA and studies of TBSS were separately performed. A whole brain template was used for the meta-analysis of WBVBA studies, while the TBSS template was applied to the meta-analysis of TBSS studies. Consistent with recent meta-analyses ([e.g. Wise et al., 2016](#_ENREF_59)), we used a random effects model. In both analyses, statistical threshold for significance was set at *p* < 0.005, with extent threshold of 10 voxels ([Nortje et al., 2013](#_ENREF_39), [Wise et al., 2016](#_ENREF_59)).

**Qualitative review regarding motion**

Given the influence of head motion during scan on DTI metrics ([Yendiki et al., 2014](#_ENREF_60)), we contacted authors of the original papers and asked whether they measured head motion and confirmed that the groups did not differ. We qualitatively review the six studies in which the authors reported that the groups did not differ significantly in head motion.

**Results**

**Systematic review**

Figure 1 summarizes study selection based on the PRISMA flowchart. Details of included studies are provided in Table 1. Twelve studies with 13 datasets, including a total of 557 individuals with ADHD and 568 TD participants, were included in the meta-analysis of TBSS studies ([Silk et al., 2009](#_ENREF_50), [Nagel et al., 2011](#_ENREF_37), [Chuang et al., 2013](#_ENREF_15), [Cortese et al., 2013](#_ENREF_18), [Adisetiyo et al., 2014](#_ENREF_1), [Van Ewijk et al., 2014](#_ENREF_58), [Cooper et al., 2015](#_ENREF_16), [De Luis-Garcia et al., 2015](#_ENREF_22), [King et al., 2015](#_ENREF_26), [O'conaill et al., 2015](#_ENREF_40), [Onnink et al., 2015](#_ENREF_42), [Yoncheva et al., 2016](#_ENREF_61)). Since one out of two datasets in Cortese et al., recruited individuals with a current ADHD diagnosis, the study was included in the analysis ([Cortese et al., 2013](#_ENREF_18)). On the other hand, 13 studies with 14 datasets with 314 individuals with ADHD and 278 TD participants were eligible for the WBVBA meta-analysis ([Ashtari et al., 2005](#_ENREF_5), [Choi et al., 2008](#_ENREF_14), [Davenport et al., 2010](#_ENREF_21), [Kobel et al., 2010](#_ENREF_27), [Konrad et al., 2010](#_ENREF_28), [Li et al., 2010](#_ENREF_30), [Peterson et al., 2011](#_ENREF_43), [Qiu et al., 2011](#_ENREF_44), [De Zeeuw et al., 2012](#_ENREF_23), [Malisza et al., 2012](#_ENREF_34), [Chaim et al., 2014](#_ENREF_10), [Lei et al., 2014](#_ENREF_29), [Chen et al., 2015](#_ENREF_13)).

**Voxel-based meta-analysis**

**TBSS studies**

As shown in Figure 2 and Table 2, AES-SDM identified four clusters in the TBSS skeleton in which FA was significantly lower in individuals with ADHD versus TD participants. The isthmus of the corpus callosum (CC) demonstrated the largest effect size and cluster extent. The cluster with the second largest effect size was situated in the right inferior fronto-occipital fasciculus (IFOF). The peak of the third largest cluster was located in the callosal radiation of the posterior midbody of the CC, extending to the upper portion of the left IFOF. The fourth largest cluster was situated in the left inferior longitudinal fasciculus (ILF).

**WBVBA studies**

Meta-analysis of WBVBA studies showed three clusters in which FA was elevated in individuals with ADHD compared to TD. The largest effect size was located in the left mid-cingulate, extending to the CC. The second largest cluster was situated in the anterior CC. The third cluster was in the left IFOF. Meta-analysis also revealed three clusters in which individuals with ADHD showed lower FA in comparison to TD. The largest was located in the anterior cingulate, while the remaining two clusters were in orbital part of the frontal lobes, bilaterally (Figure 3 & Supplementary Table 1).

**Qualitative review for motion**

We attempted to contact all authors of TBSS studies; we received responses from 11 authors corresponding to 12 TBSS studies. Six authors responded that they could not assure a lack of group differences in head motion, while authors of five studies corresponding to six datasets assured the groups did not differ significantly in head motion ([Nagel et al., 2011](#_ENREF_37), [Adisetiyo et al., 2014](#_ENREF_1), [Van Ewijk et al., 2014](#_ENREF_58), [Cooper et al., 2015](#_ENREF_16), [Yoncheva et al., 2016](#_ENREF_61)). Notably, only two of these datasets ([Nagel et al., 2011](#_ENREF_37), [Van Ewijk et al., 2014](#_ENREF_58)) found any significant between-group differences.

**Discussion**

We identified and integrated 13 TBSS datasets contrasting FA values between 557 individuals with ADHD and 568 TD controls. We then conducted a meta-analysis of 14 WBVBA datasets with 314 individuals with ADHD and 278 TD participants. Finally, integrating additional information that we gathered from investigators, we quantitatively reviewed the issue of the impact of head motion on TBSS studies. Although the number of subjects from included studies was large in both meta-analyses, results of these analyses did not converge. In individuals with ADHD, the TBSS meta-analysis showed lower FA in the posterior portions of the CC, in contrast to the WBVBA meta-analysis which revealed higher FA in anterior CC. Similarly, the TBSS studies showed lower FA in the left IFOF, while the WBVBA studies showed higher FA in a cluster in the left IFOF which was anatomically close to the one highlighted by the TBSS studies. Such inconsistencies in the direction of abnormality are not explained by the difference in analytic procedure between TBSS and WBVBA. Concerningly, in the six datasets in which groups did not differ in head motion, four studies failed to observe significant group differences.

Despite the inconsistent nature of the CC findings of WBVBA and TBSS studies, supplementary FA analyses with high-quality studies and focused on children and adolescents consistently showed atypical DTI metrics in the CC (see Supplementary Information). Involvement of the CC in ADHD pathophysiology is supported by the results of prior volumetric studies ([Seidman et al., 2005](#_ENREF_49), [Valera et al., 2007](#_ENREF_56), [Luders et al., 2009](#_ENREF_32), [Cao et al., 2010](#_ENREF_8)) and functional MRI studies that reported abnormal interhemispheric functional concordance ([e.g. Hale et al., 2014](#_ENREF_25)). Intriguingly, the relation between FA value in the CC and impulsivity or working memory was observed in TD participants and individuals with other psychiatric conditions ([Moeller et al., 2005](#_ENREF_35), [Silveri et al., 2006](#_ENREF_51), [Zahr et al., 2009](#_ENREF_62), [Liu et al., 2010](#_ENREF_31)). On the other hand, both FA and MD analyses revealed significant differences in the IFOF. Although the function of the IFOF is yet to be fully elucidated, it is believed to subserve multiple functions, including visual attention and motor planning ([reviewed in Sarubbo et al., 2013](#_ENREF_46)). The orbitofrontal area is known to be involved in regulation of emotion in decision-making and reward processing ([reviewed in Bechara, 2000](#_ENREF_6)). Given the relevance of such symptoms for ADHD, these studies indirectly support involvement of these tracts in the pathophysiology of ADHD.

Two meta-analyses of DTI studies with individuals with ADHD have been reported ([Van Ewijk et al., 2012](#_ENREF_57), [Chen et al., 2016](#_ENREF_12)). The first study integrated both WBVBA and TBSS study into a whole brain template ([Van Ewijk et al., 2012](#_ENREF_57)). This procedure is problematic because it violates the assumption under the null hypothesis that the expected difference of FA is equal at every voxel. Although the more recent study overcame this drawback, it did so by completely excluding WBVBA studies ([Chen et al., 2016](#_ENREF_12)). Thus, neither analysis considered replicability of findings across different preprocessing and analytic procedures. Further, neither analysis focused on a possible cause of artifactual results, i.e., head motion. The current meta-analysis avoided these drawbacks by conducting separate meta-analyses of TBSS studies and WBVBA studies and providing a qualitative review on possible motion effects in the TBSS studies. Surprisingly, the results of WBVBA and TBSS meta-analyses yielded opposite directionalities (higher FA in WBVBA and lower FA in TBSS) in some tracts relative to healthy comparison participants. Besides the potential influence of differences in WBVBA and TBSS preprocessing methods, the difference in locus of white matter may contribute difference in findings between WBVBA and TBSS. TBSS focuses on the center of tracts, while the large proportion of area examined by WBVBA is in the periphery of tracts. Thus, we speculate that these different loci may have different white matter pathology in central versus peripheral regions of tracts.

Concern regarding head motion and future directions

Because there is no known head motion threshold that does not yield artifactual DTI findings ([Yendiki et al., 2014](#_ENREF_60)), we focused on studies that assured the ADHD and comparison groups did not differ significantly in head motion. Four out of six such datasets reported negative findings. Further, the direction (i.e., lower FA with greater head motion) and spatial locations (e.g., anterior and posterior CC) of spurious FA findings due to motion are consistent with ADHD-related FA abnormalities observed in the present TBSS meta-analysis ([Yendiki et al., 2014](#_ENREF_60)). Such consistency raises the concern that results of DTI meta-analyses may be influenced by potential group differences in head motion. Future studies should measure motion during scan quantitatively and assure lack of group-differences in head motion. Unfortunately, available studies used different motion parameters. Since DTI preprocessing in FSL implements eddy current correction which does not register all the frames to a reference frame, absolute frame displacement is considered to reliably provide a deviation of each frame from its first time point. Further, researchers in the field should be encouraged to make vigorous effort to minimize head motion, such as implementing dental rests or bite-bars (reviewed in [Maclaren et al., 2013](#_ENREF_33), [Zaitsev et al., 2015](#_ENREF_63)). Statistical correction of motion as well as using software that corrects for motion should also be considered ([Chang et al., 2012](#_ENREF_11), [Oguz et al., 2014](#_ENREF_41)).

Limitation

The present meta-analyses have some methodological limitations. First, although it would have been preferable to use the raw unthresholded data, rather than thresholded maps, for meta-analyses ([Radua and Mataix-Cols, 2009](#_ENREF_45)), we were unable to obtain such data. In the service of enhancing rigor and reproducibility, investigators should be encouraged to make their full unthresholded statistical maps available, such as through the Open Science Framework (https://osf.io/). Second, we were not able to appropriately assess whether participants in studies that confirmed the lack of group-difference in head motion were representative of participants across all studies. For example, although the mean IQ of participants of studies that reported no group-differences in motion was similar to the mean IQ in participants in studies that did not (102 vs. 105, respectively), mean age differed (17 vs. 26 years, respectively). The male ratio of studies reporting no differences in motion was similar to studies that did not compare motion (70% vs. 62%), while percentage of stimulant-naive participants differed substantially (62% and 34%, in studies that affirmed no motion differences vs. those that did not, respectively). Although it remains unclear whether psychostimulant treatment impacts FA findings ([De Luis-Garcia et al., 2015](#_ENREF_22), [Schweren et al., 2016](#_ENREF_48)), the difference in prevalence of stimulant-naïve participants should be considered when interpreting the results of DTI studies. Additionally, it was not possible to compare the prevalence of psychiatric comorbidities or ADHD symptom severity across these studies. It should be noted that heterogeneity in these factors may contribute to the heterogeneity of findings across studies beyond the heterogeneity due to head motion issues. Further, all but one of the studies included in the present meta-analysis had male-dominant sex-distributions. Future studies should oversample females to obtain more balanced sex ratios to determine whether sex moderates findings. Finally, clinical heterogeneity of ADHD may suggest heterogeneity in neural underpinnings. Besides meta-analyses of case control studies, meta-analyses of studies adopting a dimensional approach (examining relation between symptomatology and neural underpinnings) would be informative. However, only two TBSS and three WBVBA studies ([Konrad et al., 2010](#_ENREF_28), [Peterson et al., 2011](#_ENREF_43), [Chaim et al., 2014](#_ENREF_10), [Van Ewijk et al., 2014](#_ENREF_58), [Cooper et al., 2015](#_ENREF_16)) among those included in the current meta-analysis performed voxel-level dimensional analyses, and the studies in the current meta-analysis used several different clinical measures of ADHD severity. Thus, we could not perform dimensional meta-analyses either at the voxel- or cluster-level. Future investigation adopting dimensional approaches is encouraged to complement the information from case-control studies.

Conclusion

The present meta-analysis has separately integrated TBSS and WBVBA studies. Both analyses suggested involvement of the CC in pathophysiology of ADHD, but the directions of results of these analyses were not consistent. Concerningly, such differences in FA between individuals with ADHD and TD did not appear in most of the studies that reported the lack of group differences in head motion. These results highlight the importance of controlling head motion during scanning and suggest that it is premature to draw conclusions about structural connectivity in ADHD from the extant literature.

**Key points**

Abnormal connectivity has been proposed as a key substrate of ADHD.

Diffusion tensor imaging is used to examine white matter organization.

Head motion during scan causes spurious findings in diffusion tensor imaging.

The present meta-analysis showed atypical fractional anisotropy in the corpus callosum and association fibers in ADHD compared to typically development.

However, the results were not consistent across different analytic procedures.

Studies without group differences in motion tended to report null findings.

Future studies with maximum effort to minimize head motion are warranted.

**Figure legends**

**Figure 1**: Flowchart of selection of studies.

**Figure 2**: Results of voxel-based meta-analysis of tract-based spatial statistics studies that contrast fractional anisotropy (FA) values between individuals with attention-deficit/hyperactivity disorder (ADHD) and typically developing (TD) individuals. Individuals with ADHD showed lower FA values in the callosal radiation with extension to left inferior fronto-occipital fasciculus (green), left inferior longitudinal fasciculus (yellow) (left subpanel with sagittal view), isthmus of the corpus callosum (blue), right inferior fronto-occipital fasciculus (light blue) (center subpanel with coronal view), and right superior longitudinal fasciculus (purple) (right subpanel with axial view). No brain regions showed higher FA values in individuals with ADHD compared with TD individuals.

**Figure 3:** Results of voxel-based meta-analysis of whole brain voxel based analysis studies comparing fractional anisotropy (FA) values between participants with attention-deficit/hyperactivity disorder (ADHD) and typically developing (TD) individuals. Compared with TD, individuals with ADHD showed elevated FA values in the cingulum (orange in sagittal view), posterior corpus callosum (red in coronal view) and left inferior fronto-occipital fasciculus (pink in coronal and axial views). The analysis also showed that individuals with ADHD had lower FA values compared with TD in anterior cingulate (dark blue in sagittal view), right orbitofrontal area (green in sagittal and axial views) and left orbitofrontal area (light blue in axial view).

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**Conflict of interest**

The authors declare no conflict of interest.

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