Compulsivity and impulsivity are linked to distinct aberrant developmental trajectories of fronto-striatal myelination

Gabriel Ziegler[1,2,4,*], Tobias U. Hauser[3,4,*], Michael Moutoussis[3,4], Edward T. Bullmore[5,6,7,8], Ian M. Goodyer[5,6], Peter Fonagy[9], Peter B. Jones[5,6], NSPN Consortium[10], Ulman Lindenberger[4,11] & Raymond J. Dolan[3,4]

[1] Institute of Cognitive Neurology and Dementia Research, Otto-von-Guericke-University Magdeburg, 39120 Magdeburg, Germany
[2] German Center for Neurodegenerative Diseases (DZNE), 39120 Magdeburg, Germany
[3] Wellcome Centre for Human Neuroimaging, University College London, London WC1N 3BG, United Kingdom
[4] Max Planck University College London Centre for Computational Psychiatry and Ageing Research, London WC1B 5EH, United Kingdom
[5] Department of Psychiatry, University of Cambridge, Cambridge CB2 0SZ, United Kingdom
[6] Cambridgeshire and Peterborough National Health Service Foundation Trust, Cambridge CB21 5EF, United Kingdom
[7] Medical Research Council/Wellcome Trust Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge CB2 3EB, United Kingdom
[8] ImmunoPsychiatry, GlaxoSmithKline Research and Development, Stevenage SG1 2NY, United Kingdom
[9] Research Department of Clinical, Educational and Health Psychology, University College London, London WC1E 6BT, United Kingdom
[10] A complete list of the NSPN Consortium members can be found in the supplementary information
[11] Center for Lifespan Psychology, Max Planck Institute for Human Development, Berlin, Germany
* These authors contributed equally to this work

Correspondence
Gabriel Ziegler
Institute of Cognitive Neurology and Dementia Research
German Center for Neurodegenerative Diseases (DZNE)
Otto-von-Guericke-University Magdeburg
Leipziger Str. 44
39120 Magdeburg
Germany
Phone: +49 / 391 67 250 54
Email: gabriel.ziegler@dzne.de

Tobias U. Hauser
Max Planck UCL Centre for Computational Psychiatry and Ageing Research
University College London
10-12 Russell Square
London WC1B 5EH
United Kingdom
Phone: +44 / 207 679 5264
Email: t.hauser@ucl.ac.uk

Abstract

The transition from adolescence into adulthood is a period where rapid brain development coincides with a greatly enhanced incidence of psychiatric disorder. The precise developmental brain changes that might account for this emergent psychiatric symptomatology remains obscure. Capitalising on a unique longitudinal dataset, that includes *in-vivo* myelin-sensitive magnetization transfer (MT) MRI, we show this transition period is characterised by brain-wide growth in MT, within both gray matter and adjacent juxta-cortical white matter. The expression of common developmental psychiatric risk symptomatology in this otherwise healthy population, namely compulsivity and impulsivity, was tied to regionally specific aberrant unfolding of these MT trajectories. This was most marked in superior frontal/cingulate cortex for compulsivity, and in inferior frontal/insular cortex for impulsivity. The findings highlight a brain developmental linkage for emergent psychiatric risk features, evident in regionally specific perturbations in the expansion of MT-related myelination.

Introduction

Structural brain development extends into adulthood, particularly so in regions that mediate higher cognition such as prefrontal cortex[1]. A canonical view is that this maturation is characterised by regional shrinkage in gray matter coupled to an expansion of white matter[2]. However, the underlying microstructural processes remain obscure. Two candidate mechanisms have been proposed[3], namely synaptic loss (pruning) to reduce supernumerary connections, and an increase in myelination to enhance communication efficiency. Both accounts receive some support from cross-sectional and ex-vivo studies[4–7]. There are substantial inter-individual differences in these growth trajectories[8], and the most marked changes occur within an age window where the emergence of psychiatric disorder becomes increasingly common[9,10]. This raises a possibility that psychiatric risk is tied to altered maturational brain trajectories during this critical developmental period[11,12].

Compulsivity and impulsivity are two key psychiatric dimensions[13] that show a substantial variation in expression within a 'healthy' population (Supplementary Fig. 1). At their extreme these features manifest as obsessive-compulsive disorder (OCD) and attention-deficit/hyperactivity disorder (ADHD) respectively. Macrostructural and cross-sectional studies suggest a link to deficits in fronto-striatal regions[14–17], but leave unanswered the question of whether compulsivity and impulsivity reflect consequences of aberrant developmental microstructural processes.

Here, we used quantitative structural MRI[18] to investigate how microstructural brain development unfolds during a transition into adulthood, and how individual variability in these developmental trajectories is linked to compulsive and impulsive traits. We used a novel magnetic transfer saturation (MT) imaging protocol that provides an *in-vivo* marker for macromolecules, in particular myelin[19,20]. Importantly, MT saturation has been shown to be a more direct reflection of myelin compared to other imaging protocols, such as magnetization

transfer ratio[21,22]. It also is sensitive to developmental effects[7] which renders it ideal for tracking patterns of brain maturation within longitudinal studies that involve repeated scanning of participants, a crucial feature for characterising development[23]. Using such a protocol, we show that during late adolescence and early adulthood cingulate cortex expresses the strongest myelin-related growth, both within gray and adjacent white matter. Individual differences in compulsivity are reflected in the rate of this growth in superior frontal and cingulate areas, and this contrasts with impulsivity where there is reduced myelin-related growth in lateral prefrontal cortex. Our results suggest that compulsivity and impulsivity traits within the healthy population may reflect a regionally specific consequence of differential unfolding of myelin growth trajectories.

Results

Ongoing myelin-related growth at the edge of adulthood

To assess developmental trajectories of myelin-sensitive MT, we repeatedly scanned 290 adolescents and young adults aged 14–24 years up to three times with an average follow-up time of 1.3±0.32 years (mean±SD) within an accelerated longitudinal design (1 scan: N=83, 2 scans: N=181, 3 scans: N=23). The sample was gender balanced and consisted healthy subjects (excluding self-reported illness a priori to avoid illness-related confounds, such as medication effects) that were selected to be approximately representative of the population (cf online methods for details).

Examining whole-brain maturation in gray matter revealed a brain-wide increase in myelin-related MT, with a focus within cingulate, prefrontal and temporo-parietal areas (Fig. 1a, $p<.05$ false-discovery rate [FDR] peak corrected; merging cross-sectional and longitudinal effects, separate effects shown in Supplementary Fig. 2a-b; mean±SD: 0.55±0.19% per year; max z-value voxel in posterior cingulate: 0.98% per year; Supplementary Table 1). This change was accompanied by increased MT in adjacent (juxta-cortical) superficial white matter, that was most pronounced in the same areas (Fig. 1b, mean±SD: 0.45±0.15% per year; max z-value voxel in posterior cingulate with 0.95% per year), consistent with the idea that connections in gray and white matter are myelinated in concert. Similar, albeit less pronounced, microstructural maturation was observed in subcortical areas such as posterior striatum, pallidum and dorsal thalamus (Fig. 1c). These findings highlight that myelin-related development in both cortical and subcortical areas is a marked feature of the transition from adolescence into adulthood, and likely involves both local and inter-regional fibre projections.

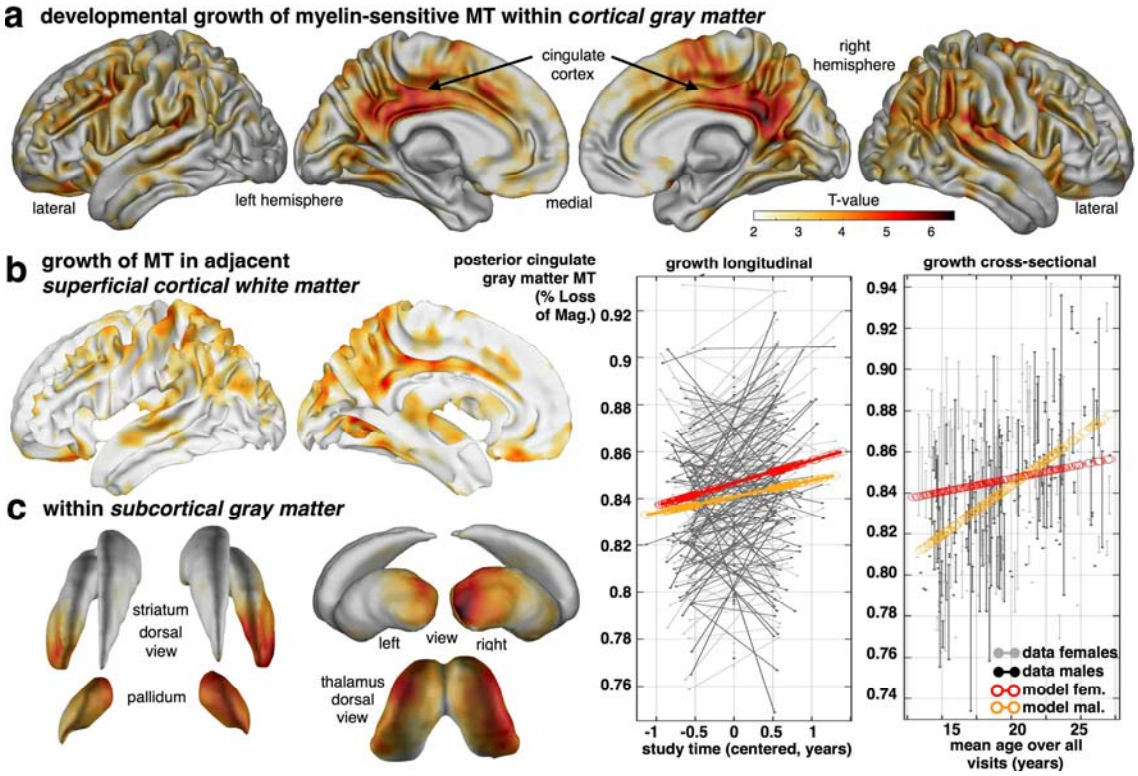

Figure 1. Developmental growth of myelin-sensitive MT into early adulthood. Transitioning into adulthood is characterised by profound increases in a myelin marker within cortical gray **(a)**, white **(b)** and subcortical gray matter **(c)**. Statistical maps of MT saturation show growth with time/visit (longitudinal) or age (cross-sectional; for specific effects of covariates, e.g. time/visit, age, sex, interactions etc., see supplementary information). **(a)** Gray matter MT growth (top row; statistical z-maps, p<.05 FDR corrected) is strongest in posterior and middle cingulate, but also present in lateral temporal, prefrontal and parietal cortex. Longitudinal model in posterior cingulate peak voxel (coloured lines in left data plot; x-axis: relative time of scan) and data (uncoloured) show an MT growth in both sexes, with a greater MT in females indicating a maturational advantage (see Supplementary Fig. 2c for region-specific sex differences, Supplementary Fig. 2d for sexual dimorphism of age-trajectories). Corresponding cross-sectional model predictions in the same region show a similar increase with age (right data plot; x-axis: mean age over visits). **(b)** MT growth in adjacent cortical white matter is most pronounced in cingulate and parieto-temporal cortex with topographical correspondence to the gray matter MT effects. **(c)** Subcortical structures express MT growth in striatum, pallidum, thalamus and hippocampus (not shown). This growth is most pronounced in posterior striatum suggesting ongoing myelin-related growth in both cortical and subcortical brain structures.

Association between macro- and microstructural development

The observed developmental expansion of myelin-sensitive MT expressed overlapping topographies with macrostructural gray matter shrinkage (with the exception of hippocampus) and white matter expansion (Fig. 2a; Supplementary Fig. 3a-d). This raises the question as to how precisely macrostructural volume change relates to development of our

myelin marker MT. A positive association in white matter volume (Fig. 2b-c; mean±SD: r=0.09±0.05) supports the notion that myelination is contributing to the observed macrostructural volume changes, as predicted by an assumption that increased myelination leads to a white matter volume expansion[24].

Voxel-wise analysis in gray matter revealed a more complex association between macrostructural development and myelination (Fig. 2b-c). We observed that the association is dependent relative to where a voxel is located in the tissue. Overall consistently negative correlations (albeit relatively small) in gray matter areas close to the white matter boundary suggest that developmental myelination may lead to a 'whitening' of gray matter, which in turn drives partial volume effects leading to a shrinkage of gray matter volume[24]. This means that gray matter volume decline in deep layers during adolescence is to some extent driven by an increase in myelination within these same areas. This negative association was found to be reduced with increased distance from the white matter boundary (Fig. 2c, bottom right panel). This suggests that ongoing myelination in superficial layers (i.e. close to the outer surface of the brain) contributes to an attenuated volume reduction, implying that developmental macrostructural change is the result of complex microstructural processes.

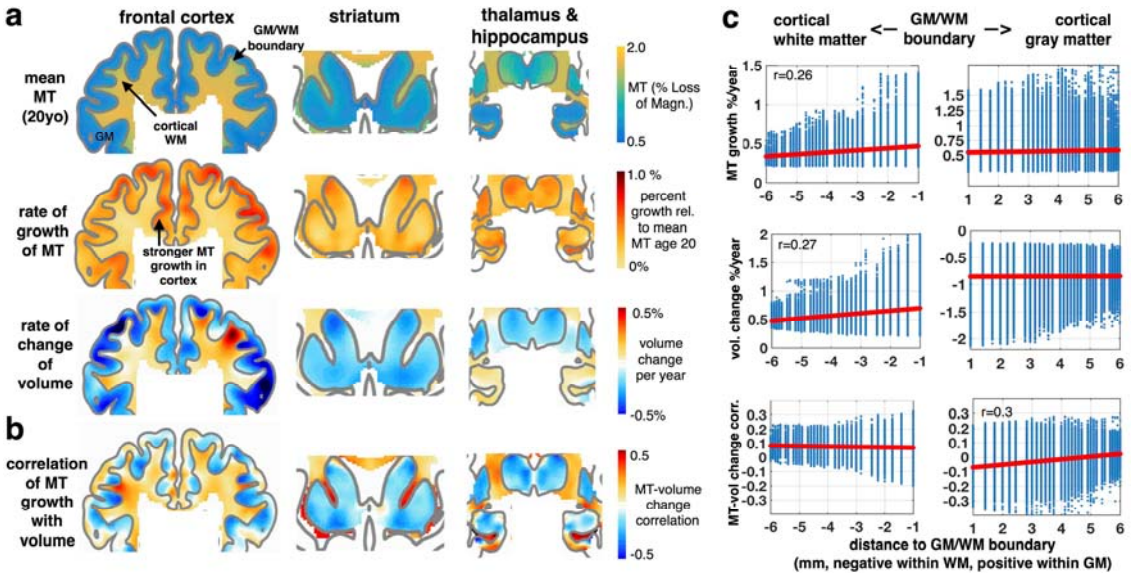

Figure 2. The relation between macrostructural and microstructural brain development. **(a)** Coronal sections through prefrontal (left panels), striatal (middle) and thalamus (right; MNI: y=15, 12, -14) show more myelin-related MT in white than in gray matter with a clearly preserved white-gray matter boundary (top row). Developmental change in MT (second row) shows an increase in myelin marker in both tissues, with a stronger growth in gray matter areas. Developmental change in macrostructural brain volume (third row) shows a characteristic cortical shrinkage (blue colours) in gray, but an expansion in white matter (red colours; cf Supplementary Fig. 3). Only hippocampal gray matter shows an opposite effect with continuing gray matter growth on the verge of adulthood. **(b)** Association between microstructural myelin growth and macrostructural volume change. A positive association throughout white matter supports the notion that myelination contributes to white matter expansion. In gray matter, a predominantly negative association in deep layers advocates for partial volume effects at the tissue boundary and positive associations in superficial layers (correlation was obtained from posterior covariance of beta parameters in sandwich estimator model simultaneously including longitudinal observations of both imaging modalities). **(c)** Association as a function of cortical depth. Microstructural growth (top row) shows consistent myelin-related growth in both tissues, but opposite macrostructural volume change (middle row). Association between micro- and macrostructural growth is positive in white matter, independent of depth. In gray matter, the mean association changes from negative in deep layers (i.e. myelin MT change associated with reduced gray matter volume) to more positive associations in superficial layers (i.e. MT associated with a tendency to more gray matter volume).

Compulsivity linked to reduced development in cingulate and striatal MT

We next asked whether individual differences in the expression of symptoms indicative of obsessive-compulsive traits are associated with distinct developmental trajectories in myelin-sensitive MT growth. We employed a dimensional approach and constructed a compound-score from two established obsessive-compulsive symptom questionnaires[25,26], using the first principal component across all items (cf. supplementary information, Supplementary Fig. 1). Top loading items of this score (subsequently called 'compulsivity') reflect compulsive behaviours, such as checking, and are tightly aligned with scores on our obsessive-compulsive questionnaires (Pearson correlations r>.8). We focused on prefrontal cortex and striatum[14] to examine how compulsivity relates to individual myelination over time. We found this trait was strongly linked to altered MT growth in superior lateral and medial frontal cortices (Fig. 3a, Supplementary Table 2), both in cortical gray and adjacent superficial white matter. Importantly, we observed that more compulsive subjects showed reduced MT growth compared to less compulsive subjects. A similar pattern was seen in ventral striatum and adjacent white matter (Fig. 3b). Intriguingly, the specific

locations of reduced MT development were spatially circumscribed in cingulate and ventral striatum, and closely align with a specific fronto-striatal loop described in primate anatomical tracing[27] studies. This suggests that compulsivity may be tied to deficient myelin-related developmental growth in this cingulate-striatal loop.

A slowing in myelination raises the question regarding the foundations this developmental change builds upon, i.e. the development-independent compulsivity effects. In principle, the observed developmental effects might be explained by opposing mechanisms. If a reduced growth builds upon a pre-existing 'hypo-myelination' then the ongoing growth reduction means that a gap widens further, amplifying existing structural differences during late adolescence. Alternatively, if a trait is linked to a 'hyper-myelination' at an early life stage, then reduced growth could reflect a 'normalisation' during development, similar to what is reported in rodents models of early life stress[28,29]. Consequently, we investigated the compulsivity main effects, and found an increased myelin-sensitive MT in similar regions of middle cingulate white matter (Fig. 3c). This suggests that compulsive subjects have a pre-existing hypermyelination in these areas, and that a reduced developmental growth leads to a 'normalisation' of this trajectory (also cf. Supplementary Fig. 4). Moreover, we found additional areas showing a compulsivity-related increase in myelin-sensitive MT, namely ventromedial prefrontal cortex and (pre-) motor areas, extending to white matter pyramidal motor tracts (Fig. 3c). These latter findings suggest that there might be additional circuits involved in compulsivity, which show only little maturation during late adolescence, but where a hypermyelination during childhood favoured the emergence of compulsive traits.

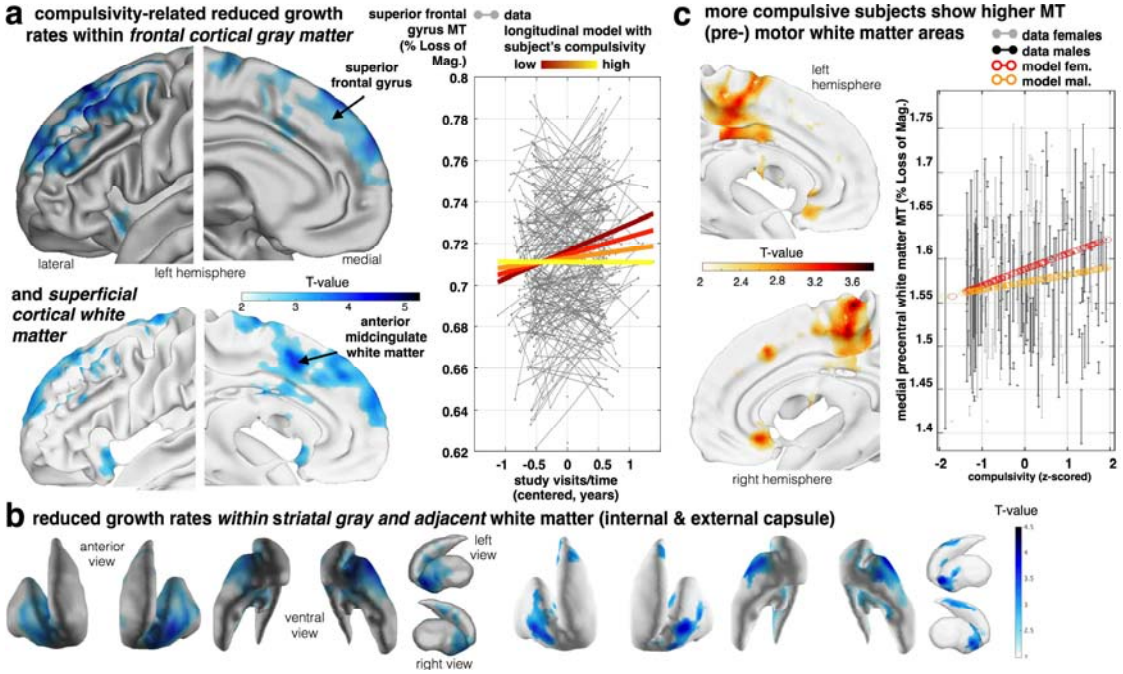

Figure 3. Compulsivity is related to reduced fronto-striatal MT growth. Longitudinal developmental change of our myelin marker is reduced in high compulsive subjects. **(a)** Aggregate compulsivity score is related to decreased MT growth in superior frontal gyrus gray matter (upper panel; z-value=5.3, p<.0022, FDR corrected) and adjacent white matter including cingulate cortex (lower panel; blue colours depicting negative time by compulsivity interactions). Subjects with higher compulsivity scores (light yellow) compared to low scoring subjects (dark red) express significantly less MT growth over visits (coloured lines in right panel indicate the interaction effect; x-axis: time of scan in years relative to each subject's mean age over visits). **(b)** The above slowing in cortical myelin-related growth is mirrored by a decreased developmental growth in subcortical ventral striatum (left panel) and the adjacent white matter (right panel). These findings indicate young people with high compulsive traits express slower maturational myelin-related change in a fronto-striatal network comprising cingulate cortex and ventral striatum. **(c)** More compulsive subjects showed locally increased baseline myelin marker (peak supplemental motor area, z-value=3.81, peak p<0.083, FDR, cluster p<0.04, FDR) in the medial wall. Right panel shows the plot of MT in this peak voxel over compulsivity (x-axis, z-scored) and with adjusted data (gray/black) and model predictions (red/orange, effects of interest: intercept, compulsivity, sex by compulsivity).

Maturation trajectories in impulsivity

We next examined whether an impulsivity trait as assessed using questionnaire scores (Barratt impulsiveness total score) was linked to individual growth of the myelin marker in fronto-striatal areas. We found that compulsivity and impulsivity traits in our sample were almost entirely independent (only sharing 1.4% common variance, Supplementary Fig. 1d), allowing us to describe their separate associations with brain development. In examining this linkage we opted to use a questionnaire measure over task-based measures of impulsivity,

because the former revealed to be more reliable, reflecting a more stable trait that is more likely to be linked to structural development. To obtain as pure a measure as possible we additionally controlled for alcohol consumption, to prevent this factor biasing our impulsivity analyses[30,31]. We found that impulsivity was associated with a widespread reduction in adolescent MT growth in lateral and medial prefrontal areas (Fig. 4a, Supplementary Table 3), effects centred on inferior frontal gyrus (IFG), the precentral sulcus and insula, both within gray and white matter.

We next assessed whether reduced myelin-related growth was also present in the striatum. We found significant associations between impulsivity and growth in MT in the dorsal striatum, more dorsal to the changes we observed for compulsivity (Fig. 4b, centred in white matter extending into gray).

This suggests that while impulsivity and compulsivity are both linked to reduced myelin-related growth in prefrontal and striatal areas, these alterations occur in distinct anatomical regions (cingulate vs IFG; ventral vs dorsal striatum). Interestingly, both compulsivity and impulsivity showed a reduced growth in the anterior insula, possibly expressing a common, transdiagnostic vulnerability.

As was the case for compulsivity, we next investigated development-independent levels of myelination in impulsivity. While compulsivity showed a prevailing 'hyper-myelination', we found that impulsivity was marked by consistent 'hypo-myelination' (Fig. 4c). The same effects were found when analysing across the entire prefrontal cortex, where a reduced MT growth reflected a risk for both psychiatric traits, whereas the baseline myelination was indicative of the specific psychiatric dimension (Supplementary Figure 4a). This suggests that a developmental hypo-myelination in impulsivity is further accentuated during late adolescent development.

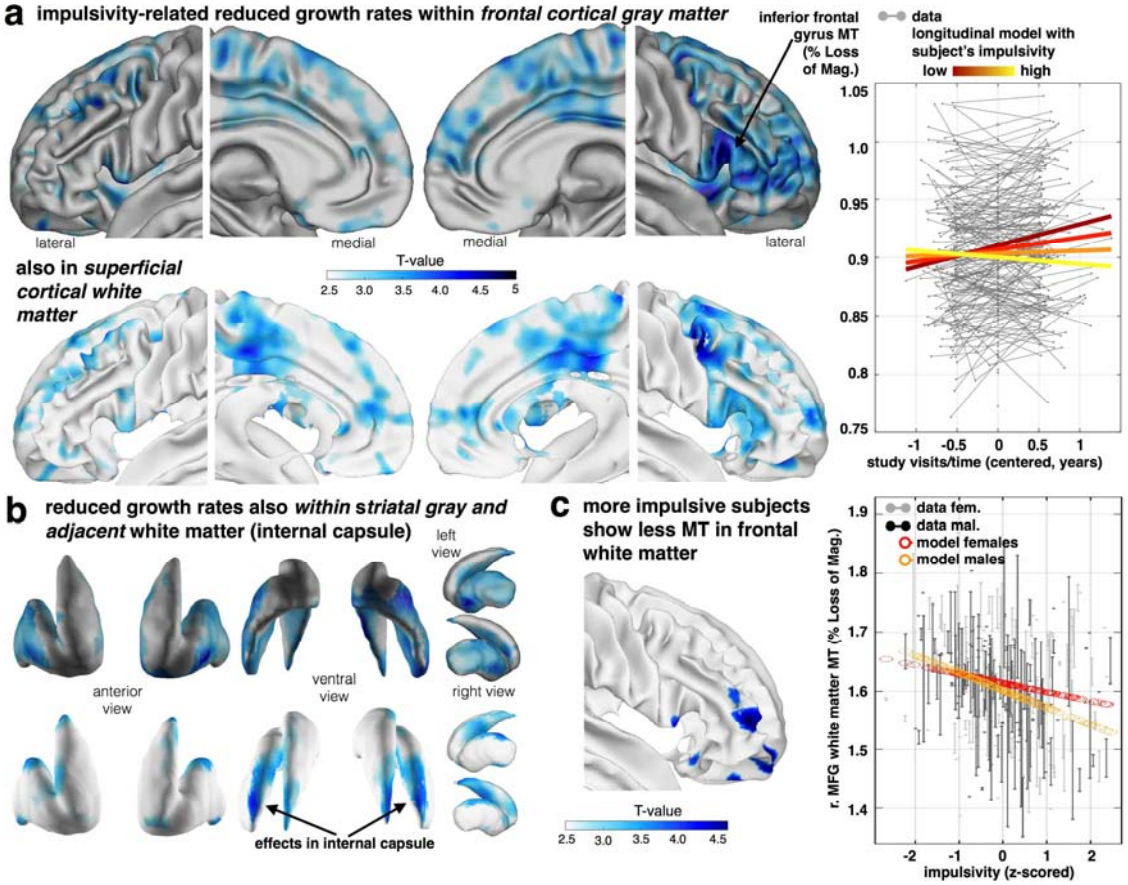

Figure 4. Decreased frontal growth in myelin-sensitive MT in impulsivity. Our myelin marker in frontal lobe is tied to impulsivity traits. **(a)** Impulsivity is associated with a reduced growth of MT in lateral (inferior and middle frontal gyrus), medial prefrontal areas (and motor/premotor and frontal pole) and anterior insula in both gray (top panel) and adjacent white matter (bottom panel) depicting negative time by impulsivity interactions (z maps, $p<.05$ FDR corrected). Plot shows that subjects with higher impulsivity (light yellow) compared to low scoring subjects (dark red) express significantly less MT growth over visits (coloured lines in right panel indicate the interaction effect; x-axis: time of scan in years relative to each subject's mean age over visits). **(b)** Similar interaction effect within striatal gray (top panel) and adjacent white matter regions (bottom panel, $p<.05$ FDR corrected). **(c)** More impulsive subjects showed locally decreased baseline myelin marker (peak middle frontal gyrus, z-value=4.33, $p<0.027$, FDR) in lateral frontal areas (for fixed other covariates time/visits, mean age of subject, sex, interactions etc.). Right panel shows the plot of MT in this peak voxel over impulsivity (x-axis, z-scored) and with adjusted data (gray/black) and model predictions (red/orange, effects of interest: intercept, impulsivity, sex by impulsivity).

Discussion

Myelin enables fast and reliable communication within, and between, neuronal populations[32,33]. Using a longitudinal, repeated-measures MRI scanning design in a unique developmental sample, we provide *in-vivo* evidence that myelination continues into adulthood as evident in a pronounced myelin-related whole-brain MT growth. We find that the macrostructural growth patterns closely resemble that expressed in our myelin marker. The positive association between these measures in white matter suggests that macrostructural volume change is, at least in part, driven by myelination. In gray matter, the depth-dependent associations suggest that macrostructural volume reduction in adolescence is the result of multiple microstructural causes. In superficial layers, an ongoing myelination seems to dampen the impact of a pruning effect leading to a slowing in measured gray matter volume decline. In deep layers close to the gray-white matter boundary, ongoing myelination may lead to an inflated estimate of volume reduction, because a myelin-induced 'whitening' of gray matter could lead to a misclassification of gray matter voxels (i.e. partial volume effects[24]), leading to an apparent volume reduction. Developmental neuroimaging with markers for specific microstructural processes may thus provide more accurate measures of the mechanisms underlying ongoing brain development.

Critically, we found that individual differences in myelin-related MT growth during development is linked to variation in the expression of individual psychiatric risk, even within this healthy sample. Both compulsivity and impulsivity are signified by a reduction in MT growth, though each is associated with distinct spatial growth trajectories. An MT growth deficiency in compulsivity is expressed in cingulate and ventral striatum, and this contrasts with a dominant dorsal striatum and lateral prefrontal focus for impulsivity. The latter area is closely implicated in impulsivity-related disorders, such as ADHD[16], and also suggested to play a critical role in attention and response inhibition[34,35]. In our study we opted

to use a relatively broad definition of impulsivity, which suggests that this area may signal general vulnerability for impulsivity. We additionally controlled for alcohol consumption, ensuring that our findings were not biased by its known effects on signatures of brain structure[36,37]. Our findings suggest that individual differences in myelin-related development are well captured by relatively broad markers for psychiatric vulnerability, but more refined cognitive endophenotypes may yield spatially more defined developmental deficits[30,31,38].

For compulsivity, we found a specific fronto-striatal network that showed decreased MT growth comprising cingulate and ventral striatum, both areas that are prime targets for invasive treatments for OCD[39,40]. Additional 'hyper-myelinated' areas might form a separate, pre-adolescent risk for compulsivity (Fig. 3c). Our findings thus highlight that an aberrant myelination trajectory in anatomically closely connected areas[27] might pose a risk for developing compulsivity disorders.

Embracing a longitudinal developmental approach, such as the one used in this study, enables one to pose distinct developmental questions. In relation to impulsivity and compulsivity, we were interested in how a stable psychiatric trait is related to ongoing, longitudinal change as well as baseline myelination differences, with the latter being indicative of influences that emerged prior to incorporation into our study. We found that regions that expressed reduced ongoing growth due to psychiatric risk features, regularly also showed a difference in baseline myelination, suggesting that a derailing of these trajectories was initiated before adolescence, but was still ongoing into early adulthood.

A further expansion of the approach described above would be to study how ongoing change in impulsivity/compulsivity relate to longitudinal brain growth. Such an analysis focuses on developmental change in a psychiatric symptom and how this relates to ongoing brain maturation (i.e. correlated change). When analysing our sample in this way, we found tendencies in the same areas that showed reduced ongoing growth (Supplementary Fig. 4c-d).

In particular, we found that subjects who became more impulsive over time, also showed reduced IFG growth. A similar tendency was observed for a change in compulsivity in medial fronto-polar areas. These findings suggest that even though compulsivity and impulsivity traits as a whole do not change at a population level at the transition into early adulthood, individual psychiatric risk trajectories show meaningful variation, and this is reflected in patterns of brain maturation.

An interesting distinction between compulsivity and impulsivity is the finding that although both show a reduced ongoing myelin-related growth, the baseline myelination patterns indicate these arise from distinct starting points. While impulsive subjects have a pre-existing prefrontal 'hypo-myelination', compulsive subjects express 'hyper-myelination' at baseline in multiple areas. This implies that in impulsivity, a developmental gap widens further, while in compulsivity the prevailing 'hyper-myelination' seems to 'normalise'. These results thus suggest that high levels of myelination are not beneficial per se, but that it is the developmental trajectory that matters most. A deviation on either side from a canonical developmental trajectory appears to pose an enhanced risk for developing psychiatric symptoms.

A key challenge for human neuroscience is to assess the cellular mechanisms that underlie macrostructural change *in-vivo*. This assumes particular importance in developmental neuroscience where longitudinal, repeated-measures, approaches are critical for understanding brain development[23]. We use a magnetization transfer (MT) saturation protocol as a proxy for myelin content, based on evidence of its sensitivity to myelin and related macromolecules[18] as well as the fact this measure is robust to instrumental biases[21]. There is also evidence for a strong relationship between MT and myelin as measured in histological studies[19,20,41] and we also showed that MT is linked with myelin gene expression[7]. Our longitudinal findings extend the importance of MT as a myelin marker with

relevance for individual differences, in so far as we show myelin-related effects are expressed in both white and gray matter, but more pronounced in the former as has been found in ex-vivo studies[4]. Taken together our findings suggest that MT is an important, albeit imperfect, indicator of myelin.

The transition into adulthood is a particularly vulnerable stage for the emergence of psychiatric illness[10]. Our findings suggest this expression is tied to ongoing microstructural brain development. The brain's potential to dynamically adjust its myelination[42], for example as a function of training[43], points to the potential of interventions that target the specific impairments. Such interventions might offer a novel therapeutic domain to lessen a developmental vulnerability to psychiatric disorder.

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Author contributions

E.T.B., I.M.G., P.F., P.B.J., NSPN Consortium, M.M, and R.J.D. designed the experiment. G.Z., T.U.H. and NSPN Consortium performed the experiment and analysed the data. G.Z., T.U.H., U.L. and R.J.D. wrote the paper.

Competing Interest

E.T.B. is employed half-time by the University of Cambridge and half-time by GlaxoSmithKline and holds stock in GlaxoSmithKline. All other authors declare no competing financial interests.

Online Methods

Study design

In total, 318 healthy adolescents and young adults were examined in this study. These subjects belonged to an MRI branch of a larger study focusing on psychiatric traits during development (NSPN study[44], cf supplementary information). The subjects were recruited in an accelerated longitudinal study design with 6 age bins between 14 and 24 years with roughly equal number of subjects per bin, and equal gender and ethnicity (age mean (std) 19.45 (2.85) years). Subjects were recruited in London and Cambridgeshire, selected from a larger questionnaire cohort with over 2400 subjects, after screening out subjects with self-reported pervasive neurological, developmental or psychiatric disorders. We analysed 514 available brain scans from 290 healthy individuals that passed quality control. In particular, data from 83, 181, and 23 subjects with one, two or three visits per person were available, with mean (standard deviation) follow-up interval of 1.3 (0.32) years between first and last visit. The study was approved by the UK National Research Ethics Service and all participants (if <16y also their legal guardian) gave written informed consent.

Assessing compulsivity and impulsivity

To examine the effects of compulsivity and impulsivity traits on myelin development, we collected self-report questionnaires along with the MRI assessments. As an index of impulsivity, we used the Barratt Impulsiveness Scale (BIS)[45] total score, a well-established and calibrated measure to assess general impulsivity. To assess compulsivity, we built a composite score (using principal component analysis, cf supplementary information) from two established obsessive-compulsive questionnaires (Supplementary Fig. 1, revised Obsessive-Compulsive Inventory[26], revised Padua Inventory[25]). Compulsivity and impulsivity trait measures showed a very minor correlation r=0.119 in the large behavioural

sample, supporting a notion of rather independent dimensions (less than 1.4% shared variance). Linear mixed-effects modelling (LME) revealed that both indices did not substantially change during the study period, which is why we used aggregate scores (LME intercepts) for most of the subsequent MRI analyses (cf supplementary information).

MRI data acquisition and longitudinal preprocessing

Brain scans were acquired using the quantitative MPM protocol[46] on three 3T Siemens Magnetom TIM Trio MRI systems located in Cambridge and London. Isotropic 1mm MT maps were collected to quantify local changes in gray and adjacent white matter and all analyses were performed using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm), the Voxel-Based Quantification (VBQ) toolbox for SPM[47,48], and custom made tools.

Magnetization transfer saturation (MT) maps provide quantitative maps for myelin and related macro-molecules, and correlate highly with myelin content in histological studies[19,20]. MT thus overcomes the limitations of previous methods to measure white matter integrity, such as diffusion tensor imaging, that are insensitive to attribute changes in diffusivity to actual microstructural changes such as myelin[49] and outperforms earlier protocols such as magnetization transfer ratio[21].

To assess the microstructural myelin-related MT changes during development, we used a longitudinal processing pipeline that follows the following steps (details cf supplementary information). To normalise the images, we performed a symmetric diffeomorphic registration for longitudinal MRI[50] and subsequently segmented each midpoint image into gray matter (GM), white matter (WM) and cerebrospinal fluid using the computational anatomy toolbox. MT maps from all time-points were then normalized to MNI space using geodesic shooting[51,52], spatially smoothed preserving GM/WM tissue boundaries,

and manually as well as statistically inspected (using sample covariance-based sample homogeneity measures, CAT12 toolbox SPM). Lastly, we constructed masks for both gray and adjacent white matter using anatomical atlases for subsequent analysis (cf. illustrated in Fig. 2). As compulsivity and impulsivity are primarily associated with deficits in frontal and striatal networks[14], we constrained the analyses of these psychiatric dimensions to striatal and prefrontal regions (cf supplementary information).

To relate these quantitative (VBQ) to more conventional metrics (i.e. Voxel-Based Morphometry), we normalized tissue segment maps accounting for existing differences and ongoing changes of local volumes using within- and between-subjects modulation. The obtained maps were spatially smoothed (6 mm FWHM).

Longitudinal MT analyses

In this study, we employed a longitudinal observational design to explore myelin-related MT development in late adolescence and early adulthood. Traditional cross-sectional approaches employ between-subject measures to study age-related differences rather than within-subject changes. These can be affected by biases[53], such as cohort differences[54,55] or selection bias[56], and typically require additional assumptions, such as (a) the age-related effect in the sample is an unbiased estimate of the group level average of individual within-subject effects or (b) all subjects change in the same way. Here, we follow recent analysis recommendations[57], taking the advantage of the accelerated longitudinal design in which we study separately (in one joint model) (a) how the individual brain changes over time (from baseline to follow up(s)) and (b) how it varies with mean age of different subjects in the study, and their interaction. To do so, we used the accurate and efficient Sandwich Estimator (SwE)[57] method for voxel-based longitudinal image analysis (http://warwick.ac.uk/tenichols/SwE; cf supplementary information). Similar to common

cross-sectional GLM approaches, this so-called marginal model describes expected variability as a function of predictors in a design matrix, while additionally accounting for correlations due to repeated measurements and unexplained variations across individuals as an enriched error term.

In our developmental analyses, we focused on the factors time/visits and mean age of the individual (over all visits) on whole-brain networks. Moreover, in order to investigate if and how compulsivity and impulsivity traits are related to brain trajectories and altered growth in fronto-striatal networks, we enriched the models by adding a main effect trait (compulsivity/impulsivity) as well as their interaction with change over time/visits. The latter metric allows to assess how MT growth is associated with compulsivity and impulsivity trait (e.g. lower MT growth in high compulsives), whereas the former indicates how a trait relates to overall MT differences across individuals, independent of all other covariates (time, mean age of a subject over all scans, sex, etc.). Unless mentioned otherwise, all analyses were performed in a dimensional way, using the subjects' trait scores. For illustration purposes, we subsequently used group-splits to visualise models and data.

Notably, in addition to including effects time/visit, mean age of subject (further denoted age_mean), and compulsivity/impulsivity traits, all presented models were tested for indications of effects of (a) other relevant demographic factors, especially sex and socioeconomic status; (b) non-linearites (accelerations/deceleration) of brain changes (across the study age range) and of age-related trajectories, especially using time by age_mean interactions, and quadratic/cubic effects of age_mean; and (c) all first order interactions among all previous covariates (cf. supplementary information for more details). No indications for substantial non-linearities were observed for myelin-sensitive MT (cf Fig. S2e) but for volumes (cf Fig. S3c). Demographic covariates and confounds (total intracranial volume, scanner, socioeconomic status) were included in all models, and additional

interactions of covariates were included when showing significant effects. This is intended to account for potential confounding effects of residual head size variations induced by tissue-weighted smoothing of quantitative MT analysis and during morphometric analysis. Additionally this allows using a consistent design (and power) across modalities. We controlled for the False Discovery Rate (FDR) during corrections for multiple comparisons in all image analyses. All correlations were reported without p-values in accordance with the recommendations from the American Statistical Association[58], but given the sample size, the reader rests assured that these would be significant if tested.

We additionally tested for correlated changes in the supplementary material, investigating how a change in compulsivity/impulsivity relates to ongoing myelin-related changes (cf. Supplementary Information for details).

Macrostructural changes

To be able to relate the findings from our microstructural myelin marker (MT) to traditional macrostructural markers (GM/WM volume), we performed analogue analyses (using Voxel-based Morphometry, VBM[59]) as described above on traditional normalized tissue segment maps. To quantify how developmental changes of macro- to microstructural parameters correlate, we specified a multi-modal SwE model including all volumetric and MT scans in a joint (blockdiagonal) design matrix with all covariates separately for each modality. Developmental effects within each modality are defined by respective *time/visit* and *age_mean* beta estimates of those regressors of the design matrix. After SwE model estimation, the posterior covariance of these beta parameters from volume and MT modalities were calculated and transformed into correlation (see Fig. 2b).

Assessing wide-spread effects of compulsivity and impulsivity

To assess the effects of development and compulsivity/impulsivity on myelin-sensitive MT across the entire frontal lobe (GM, WM separately), we used linear mixed-effects modelling (LME, cf supplementary information). Besides assessing the effects of *time/visit* and *time* by (continuous) *trait* interactions, we calculated the model predictions over the study period while accounting for variations of mean age across individuals[60]. Random-effect intercepts were included and proved optimally suited using likelihood ratio tests. To assess myelin marker differences at baseline we calculated t-statistics (and p-values) of main effect of traits.

References

1. Gogtay, N. *et al.* Dynamic mapping of human cortical development during childhood through early adulthood. *Proc. Natl. Acad. Sci. U. S. A.* **101,** 8174–8179 (2004).
2. Sowell, E. R., Thompson, P. M., Holmes, C. J., Jernigan, T. L. & Toga, A. W. In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. *Nat. Neurosci.* **2,** 859–861 (1999).
3. Paus, T. Growth of white matter in the adolescent brain: myelin or axon? *Brain Cogn.* **72,** 26–35 (2010).
4. Miller, D. J. *et al.* Prolonged myelination in human neocortical evolution. *Proc. Natl. Acad. Sci. U. S. A.* **109,** 16480–16485 (2012).
5. Perrin, J. S. *et al.* Growth of white matter in the adolescent brain: role of testosterone and androgen receptor. *J. Neurosci. Off. J. Soc. Neurosci.* **28,** 9519–9524 (2008).
6. Petanjek, Z. *et al.* Extraordinary neoteny of synaptic spines in the human prefrontal cortex. *Proc. Natl. Acad. Sci. U. S. A.* **108,** 13281–13286 (2011).
7. Whitaker, K. J. *et al.* Adolescence is associated with genomically patterned consolidation of the hubs of the human brain connectome. *Proc. Natl. Acad. Sci.* **113,** 9105–9110 (2016).
8. Foulkes, L. & Blakemore, S.-J. Studying individual differences in human adolescent brain development. *Nat. Neurosci.* (2018). doi:10.1038/s41593-018-0078-4
9. Kessler, R. C. *et al.* Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World Psychiatry Off. J. World Psychiatr. Assoc. WPA* **6,** 168–176 (2007).
10. Paus, T., Keshavan, M. & Giedd, J. N. Why do many psychiatric disorders emerge during adolescence? *Nat. Rev. Neurosci.* **9,** 947–957 (2008).

11. McCarthy, H. *et al.* Attention network hypoconnectivity with default and affective network hyperconnectivity in adults diagnosed with attention-deficit/hyperactivity disorder in childhood. *JAMA Psychiatry* **70,** 1329–1337 (2013).
12. Douaud, G. *et al.* A common brain network links development, aging, and vulnerability to disease. *Proc. Natl. Acad. Sci.* **111,** 17648–17653 (2014).
13. Chamberlain, S. R., Stochl, J., Redden, S. A. & Grant, J. E. Latent traits of impulsivity and compulsivity: toward dimensional psychiatry. *Psychol. Med.* 1–12 (2017). doi:10.1017/S0033291717002185
14. Robbins, T. W., Gillan, C. M., Smith, D. G., de Wit, S. & Ersche, K. D. Neurocognitive endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry. *Trends Cogn. Sci.* **16,** 81–91 (2012).
15. de Wit, S. J. *et al.* Multicenter voxel-based morphometry mega-analysis of structural brain scans in obsessive-compulsive disorder. *Am. J. Psychiatry* **171,** 340–349 (2014).
16. Norman, L. J. *et al.* Structural and functional brain abnormalities in attention-deficit/hyperactivity disorder and obsessive-compulsive disorder: A comparative meta-analysis. *JAMA Psychiatry* **73,** 815–825 (2016).
17. Carlisi, C. O. *et al.* Comparative multimodal meta-analysis of structural and functional brain abnormalities in autism spectrum disorder and obsessive-compulsive disorder. *Biol. Psychiatry* (2016). doi:10.1016/j.biopsych.2016.10.006
18. Weiskopf, N., Mohammadi, S., Lutti, A. & Callaghan, M. F. Advances in MRI-based computational neuroanatomy: from morphometry to in-vivo histology. *Curr. Opin. Neurol.* **28,** 313–322 (2015).
19. Schmierer, K., Scaravilli, F., Altmann, D. R., Barker, G. J. & Miller, D. H. Magnetization transfer ratio and myelin in postmortem multiple sclerosis brain. *Ann. Neurol.* **56,** 407–415 (2004).

20. Turati, L. *et al.* In vivo quantitative magnetization transfer imaging correlates with histology during de- and remyelination in cuprizone-treated mice. *NMR Biomed.* **28,** 327–337 (2015).
21. Callaghan, M. F., Helms, G., Lutti, A., Mohammadi, S. & Weiskopf, N. A general linear relaxometry model of R1 using imaging data. *Magn. Reson. Med.* **73,** 1309–1314 (2015).
22. Campbell, J. S. W. *et al.* Promise and pitfalls of g-ratio estimation with MRI. *NeuroImage* (2017). doi:10.1016/j.neuroimage.2017.08.038
23. Raz, N. & Lindenberger, U. Only time will tell: cross-sectional studies offer no solution to the age-brain-cognition triangle: comment on Salthouse (2011). *Psychol. Bull.* **137,** 790–795 (2011).
24. Paus, T. Mapping brain maturation and cognitive development during adolescence. *Trends Cogn. Sci.* **9,** 60–68 (2005).
25. Burns, G. L., Keortge, S. G., Formea, G. M. & Sternberger, L. G. Revision of the Padua Inventory of obsessive compulsive disorder symptoms: Distinctions between worry, obsessions, and compulsions. *Behav. Res. Ther.* **34,** 163–173 (1996).
26. Foa, E. B. *et al.* The Obsessive-Compulsive Inventory: Development and validation of a short version. *Psychol. Assess.* **14,** 485–496 (2002).
27. Haber, S. N. Corticostriatal circuitry. *Dialogues Clin. Neurosci.* **18,** 7–21 (2016).
28. Bath, K., Manzano-Nieves, G. & Goodwill, H. Early life stress accelerates behavioral and neural maturation of the hippocampus in male mice. *Horm. Behav.* **82,** 64–71 (2016).
29. Wiggins, R. C. & Gottesfeld, Z. Restraint stress during late pregnancy in rats elicits early hypermyelination in the offspring. *Metab. Brain Dis.* **1,** 197–203 (1986).
30. Whelan, R. *et al.* Adolescent impulsivity phenotypes characterized by distinct brain networks. *Nat. Neurosci.* **15,** 920–925 (2012).

31. Holmes, A. J., Hollinshead, M. O., Roffman, J. L., Smoller, J. W. & Buckner, R. L. Individual Differences in Cognitive Control Circuit Anatomy Link Sensation Seeking, Impulsivity, and Substance Use. *J. Neurosci. Off. J. Soc. Neurosci.* **36,** 4038–4049 (2016).

32. Virchow, R. Ueber das ausgebreitete Vorkommen einer dem Nervenmark analogen Substanz in den thierischen Geweben. *Arch. Für Pathol. Anat. Physiol. Für Klin. Med.* **6,** 562–572 (1854).

33. Bunge, R. P. Glial cells and the central myelin sheath. *Physiol. Rev.* **48,** 197–251 (1968).

34. Rubia, K. 'Cool' inferior frontostriatal dysfunction in attention-deficit/hyperactivity disorder versus 'hot' ventromedial orbitofrontal-limbic dysfunction in conduct disorder: a review. *Biol. Psychiatry* **69,** e69-87 (2011).

35. Criaud, M. & Boulinguez, P. Have we been asking the right questions when assessing response inhibition in go/no-go tasks with fMRI? A meta-analysis and critical review. *Neurosci. Biobehav. Rev.* **37,** 11–23 (2013).

36. Whelan, R. *et al.* Neuropsychosocial profiles of current and future adolescent alcohol misusers. *Nature* **512,** 185–189 (2014).

37. O'Halloran, L., Nymberg, C., Jollans, L., Garavan, H. & Whelan, R. The potential of neuroimaging for identifying predictors of adolescent alcohol use initiation and misuse. *Addict. Abingdon Engl.* **112,** 719–726 (2017).

38. Boedhoe, P. S. W. *et al.* Distinct Subcortical Volume Alterations in Pediatric and Adult OCD: A Worldwide Meta- and Mega-Analysis. *Am. J. Psychiatry* appiajp201616020201 (2016). doi:10.1176/appi.ajp.2016.16020201

39. Dougherty, D. D. *et al.* Prospective long-term follow-up of 44 patients who received cingulotomy for treatment-refractory obsessive-compulsive disorder. *Am. J. Psychiatry* **159,** 269–275 (2002).

40. Figee, M. *et al.* Deep brain stimulation restores frontostriatal network activity in obsessive-compulsive disorder. *Nat. Neurosci.* **16,** 386–387 (2013).

41. Mottershead, J. P. *et al.* High field MRI correlates of myelin content and axonal density in multiple sclerosis--a post-mortem study of the spinal cord. *J. Neurol.* **250,** 1293–1301 (2003).

42. Franklin, R. J. M. & ffrench-Constant, C. Remyelination in the CNS: from biology to therapy. *Nat. Rev. Neurosci.* **9,** 839–855 (2008).

43. Sampaio-Baptista, C. *et al.* Motor skill learning induces changes in white matter microstructure and myelination. *J. Neurosci. Off. J. Soc. Neurosci.* **33,** 19499–19503 (2013).

44. Kiddle, B. *et al.* Cohort profile: The NSPN 2400 Cohort: a developmental sample supporting the Wellcome Trust NeuroScience in Psychiatry Network. *Int. J. Epidemiol.* (2017). doi:10.1093/ije/dyx117

45. Patton, J. H., Stanford, M. S. & Barratt, E. S. Factor structure of the Barratt impulsiveness scale. *J. Clin. Psychol.* **51,** 768–774 (1995).

46. Weiskopf, N. *et al.* Quantitative multi-parameter mapping of R1, PD*, MT, and R2* at 3T: a multi-center validation. *Front. Neurosci.* **7,** (2013).

47. Callaghan, M. F. *et al.* Widespread age-related differences in the human brain microstructure revealed by quantitative magnetic resonance imaging. *Neurobiol. Aging* **35,** 1862–1872 (2014).

48. Draganski, B. *et al.* Regional specificity of MRI contrast parameter changes in normal ageing revealed by voxel-based quantification (VBQ). *NeuroImage* **55,** 1423–1434 (2011).

49. Jones, D. K., Knösche, T. R. & Turner, R. White matter integrity, fiber count, and other fallacies: The do's and don'ts of diffusion MRI. *NeuroImage* **73,** 239–254 (2013).

50. Ashburner, J. & Ridgway, G. R. Symmetric diffeomorphic modeling of longitudinal structural MRI. *Front. Neurosci.* **6,** 197 (2012).

51. Ashburner, J. A fast diffeomorphic image registration algorithm. *NeuroImage* **38,** 95–113 (2007).

52. Ashburner, J. & Friston, K. J. Diffeomorphic registration using geodesic shooting and Gauss–Newton optimisation. *NeuroImage* **55,** 954–967 (2011).

53. Neuhaus, J. M. & Kalbfleisch, J. D. Between- and Within-Cluster Covariate Effects in the Analysis of Clustered Data. *Biometrics* **54,** 638–645 (1998).

54. Hoffman, L., Hofer, S. M. & Sliwinski, M. J. On the confounds among retest gains and age-cohort differences in the estimation of within-person change in longitudinal studies: a simulation study. *Psychol. Aging* **26,** 778–791 (2011).

55. Sliwinski, M., Hoffman, L. & Hofer, S. M. Evaluating Convergence of Within-Person Change and Between-Person Age Differences in Age-Heterogeneous Longitudinal Studies. *Res. Hum. Dev.* **7,** 45–60 (2010).

56. Lash, T. L., Fox, M. P. & Fink, A. K. *Applying Quantitative Bias Analysis to Epidemiologic Data*. (Springer, 2009).

57. Guillaume, B. *et al.* Fast and accurate modelling of longitudinal and repeated measures neuroimaging data. *NeuroImage* **94,** 287–302 (2014).

58. Wasserstein, R. L. & Lazar, N. A. The ASA's Statement on p-Values: Context, Process, and Purpose. *Am. Stat.* **70,** 129–133 (2016).

59. Ashburner, J. & Friston, K. J. Voxel-based morphometry--the methods. *NeuroImage* **11,** 805–821 (2000).

60. Gelman, A. *et al. Bayesian Data Analysis, Third Edition*. (Chapman and Hall/CRC, 2013).