Compulsivity and impulsivity traits linked to attenuated developmental fronto-striatal myelination trajectories

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Abstract

A transition from adolescence into adulthood corresponds to a period where rapid brain development coincides with an enhanced incidence of psychiatric disorder. The precise developmental brain changes that account for this emergent psychiatric symptomatology remain obscure. Capitalising on a unique longitudinal dataset, that includes *in-vivo* myelin-sensitive magnetization transfer (MT) MRI, we show that coming of age is characterised by brain-wide growth in MT, within both gray matter and adjacent juxta-cortical white matter. In this healthy population the expression of common developmental traits, namely compulsivity and impulsivity, are tied to a reduced unfolding of these MT trajectories in fronto-striatal regions. This reduction is most marked in dorsomedial and dorsolateral frontal structures for compulsivity, and in lateral and medial frontal areas for impulsivity. The findings highlight a brain developmental linkage for compulsivity and impulsivity is evident in regionally specific reduced unfolding 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 (GM) coupled to an expansion of white matter (WM)[2]. However, the underlying microstructural processes remain obscure. Two candidate mechanisms are proposed[3], namely synaptic loss (pruning) that reduces supernumerary connections, and an increase in myelination that serves to enhance communication efficiency. Both accounts receive a degree of support from cross-sectional and ex-vivo studies[4–7]. What is also known is that there are substantial inter-individual differences in these growth trajectories[8], with the most marked changes occurring within an age window where an emergence of psychiatric illness is increasingly common[9,10]. This raises a possibility that this enhanced psychiatric risk is tied to altered maturational brain trajectories during this critical developmental period[11,12].

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

Here we used semi-quantitative structural MRI[18] to investigate how microstructural brain development unfolds during a transition into adulthood, specifically asking whether individual variability in these developmental brain trajectories is linked to the expression of compulsive and impulsive traits. We used a novel magnetic transfer saturation (MT) imaging protocol to provide 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 is also sensitive to developmental effects[7]. This renders it ideal for tracking patterns of brain maturation in longitudinal studies involving repeated scanning of participants, a crucial necessity for a full characterisation of development[23]. Using such a protocol, we show that during late adolescence and early adulthood cingulate cortex expresses the greatest myelin-related growth, both within gray and adjacent white matter. Individual differences in compulsivity are reflected in a reduced rate of this growth particularly within dorsomedial and dorsolateral frontal regions. This contrasted with impulsivity, which was associated with reduced myelin-related growth in lateral and medial prefrontal cortex. Our results suggest that within an otherwise healthy population heterogeneity, compulsivity and impulsivity traits reflect regionally distinct differential unfolding in myelin growth trajectories.

Results

Ongoing myelin-related growth at the edge of adulthood

To assess developmental trajectories of myelin-sensitive MT we exploited an accelerated longitudinal design that included repeated scanning in 295 adolescents and young adults aged 14–24 years, up to three times in all, with an average follow-up time of 1.3±0.32 years (mean±SD) (1 scan: N=99, 2 scans: N=169, 3 scans: N=21). The sample was gender balanced and comprised of otherwise healthy subjects (excluding self-reported illness a priori to avoid illness-related confounds, such as medication effects) who were selected to be approximately representative of the population (cf online methods for details).

Examining individual, ongoing maturation using whole-brain voxel-based quantification analyses (Supplementary Fig. 2a-b) in gray matter revealed a brain-wide increase in myelin-related MT, with a strong emphasis within cingulate, prefrontal and temporo-parietal areas (Fig. 1a, p<.05 false-discovery rate [FDR] peak corrected; merging cross-sectional and longitudinal effects, mean change in GM (±SD): 0.58±0.19% per year; max z-value voxel [z=6.78, p<.002 FDR] in right angular gyrus [MNI: 51 -46 44]: 0.98% per year; cf. Supplementary Table 1 for parametric and non-parametric results; separate cross-sectional and longitudinal effects shown in Supplementary Fig. 3a-b). These developmental changes were accompanied by increased MT in adjacent (juxta-cortical) superficial white matter with a similar topography to that seen in gray matter (Fig. 1b, mean change: 0.47±0.18% per year; max z-value voxel [z=6.18, p<.004 FDR] in posterior cingulate [5 -58 56] with 0.89% per year; cf. Supplementary Table 1), consistent with the idea that connections within gray and white matter are myelinated in concert (correlation between neighbouring gray-/white-matter voxels: r=0.25, permutation p<0.001; cf. online methods). Similar, albeit less pronounced, microstructural maturation was observed in subcortical gray matter nuclei including amygdala, ventral and posterior striatum, pallidum and dorsal

thalamus (Fig. 1c, mean change: 0.29±0.06% per year; max z-value voxel [z=5.12, p<.004 FDR] in amygdala [25 4 -23] with 0.5% per year). These findings highlight that myelin-related MT development in both cortical and subcortical areas is a marked feature of a transition from adolescence into adulthood, and conforms to a pattern that is suggestive of involvement of both local and inter-regional fibre projections.

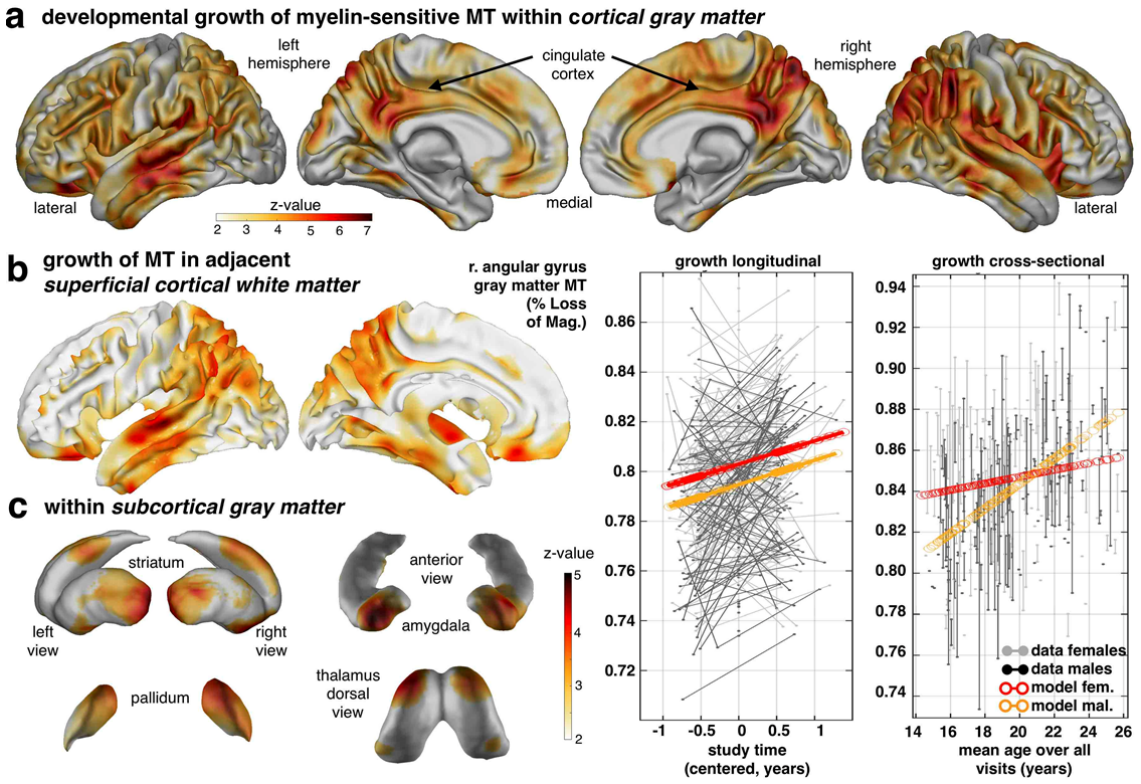

Figure 1. Developmental growth of myelin-sensitive MT into early adulthood. Transitioning into adulthood is characterised by marked increases in a myelin marker within cortical gray **(a)**, white **(b)** and subcortical gray matter **(c)**. Statistical maps of voxel-wise MT saturation show growth with 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, sampling-based correction reported in Supplementary Table 1, cf Supplementary Fig. 2c) is strongest in parietal, lateral temporal, posterior and middle cingulate, but is also present in prefrontal cortex. Longitudinal model in angular gyrus peak (mean across a 6mm sphere; coloured lines in left data plot; x-axis: relative time of scan) and data (uncoloured) shows an MT growth in both sexes, with a marked sex difference reflecting greater MT in females (see Supplementary Fig. 3c for region-specific sex differences). 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 a coarse topographical correspondence to the gray matter MT effects. **(c)** Subcortical gray matter nuclei express MT age effects in striatum, pallidum, thalamus, amygdala and

hippocampus (cf Fig. 2a-b). This growth is most pronounced in amygdala, ventral (max z-value voxel [z=4.81, p=.004 FDR], [MNI: 20 13 -11]) and posterior (z=4.47, p=0.004 FDR, [MNI: -31 -19 3]) striatum suggesting ongoing myelin-associated changes 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. 4a-c and Supplementary Table 4 for macrostructural results). This raises a 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, t=453, p<e-15) supports the notion that myelination is linked to the observed macrostructural volume changes, as predicted by an assumption that increased myelination leads to a white matter volume expansion[24]. The relatively modest, but consistent, effect size is partially explained on the basis that we only investigate the purely developmental associations and controlled for potentially confounding effects. However, our findings leave open a possibility that there might be additional microstructural factors driving the change in white matter macrostructure.

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 on where a voxel is located in the tissue. An overall profile of consistently negative correlations (albeit relatively small) in gray matter zones close to the white matter boundary (0-2mm from GM/WM border: t=300, p<e-15) suggest that developmental myelination may lead to a 'whitening' of gray matter, which in turn is likely to drive partial volume effects evident in a shrinkage of gray matter volume[24,25]. This means that a gray matter volume decline in deep layers during adolescence may well be driven by an increase

in myelination within these same areas. This negative association was reduced with increased distance from the white matter boundary (r=0.3, p<e-15, 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 and implies that developmental macrostructural change is the result of complex microstructural processes.

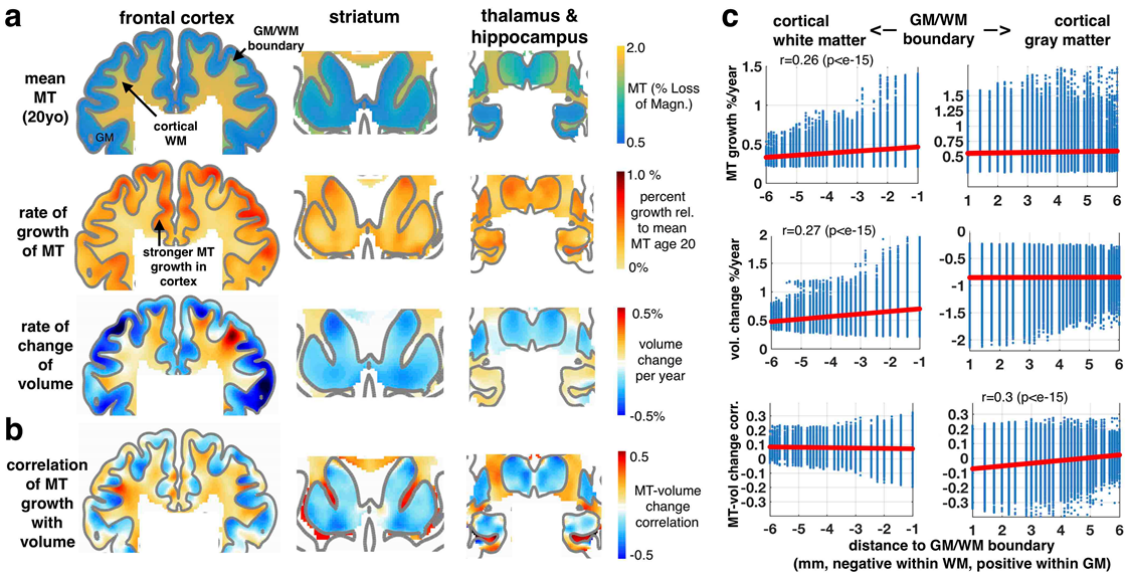

Figure 2. The relation between macrostructural and microstructural brain development. **(a)** Coronal sections through prefrontal (left panels), striatal (middle) and thalamus/hippocampus (right; MNI: y=15, 12, -14) show more myelin-related MT in white than in gray matter with a clearly preserved white-gray 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 core and frontal white matter (red colours; cf Supplementary Fig. 4). Only hippocampal gray matter shows an opposite effect with continuing gray matter growth up to the verge of adulthood. **(b)** Association between microstructural myelin growth and macrostructural volume change. A positive association throughout whole-brain white matter supports the notion that myelination contributes to white matter expansion. In gray matter, a predominantly negative association in deep layers points to 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 Euclidean distance to GM/WM boundary. 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 distance. 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, dorsolateral and striatal MT

We next asked whether individual differences in the expression of symptoms, indicative of obsessive-compulsive traits, were associated with distinct developmental trajectories in myelin-sensitive MT growth. We employed a dimensional approach exploiting a heterogeneity within this otherwise healthy community sample. We computed a compound-score (first principal component, Supplementary Fig. 1a-f) from the two established obsessive-compulsive symptom questionnaires[26,27] available in our sample in order to aggregate a common score to index meaningful variation (cf. Supplementary Fig. 1). Top loading items on this score (subsequently called 'compulsivity') reflect compulsive behaviours, such as checking, and it was strongly aligned with total scores on our obsessive-compulsive questionnaires (Pearson correlations r>.8).

Assessing how compulsivity related to individual myelination over time, we found our compulsive measure was linked to altered MT growth primarily in frontal areas, with significant clusters in dorsolateral (superior frontal gyrus, GM: z=4.87, p=.009 FDR, [-23 34 49], WM: z=4.28, p<.05 FDR, [-24 -4 64]) and dorsomedial (anterior mid-cingulate, GM: z=4.1, p=.009 FDR, [18 1 58], WM: z=3.74, p<.05 FDR, [-25 1 37]) frontal cortices (Fig. 3a, Supplementary Table 2), both in cortical gray and adjacent superficial white matter. Importantly, more compulsive subjects showed reduced MT growth compared to less compulsive subjects. A similar pattern was seen in the left ventral striatum (z=3.9, p=.018 FDR, [-22 14 -9]) and adjacent white matter (z=4.2, p=.027 FDR, [21 -9 25], Fig. 3b). Intriguingly, the locations of reduced MT development were spatially centred in cingulate and ventral striatum, and this regional focus aligns with a specific fronto-striatal loop

described in primate anatomical tracing[28] studies. This alignment with a well described anatomical circuit suggests compulsivity may relate to attenuated myelin-related developmental growth in this cingulate-striatal loop[14].

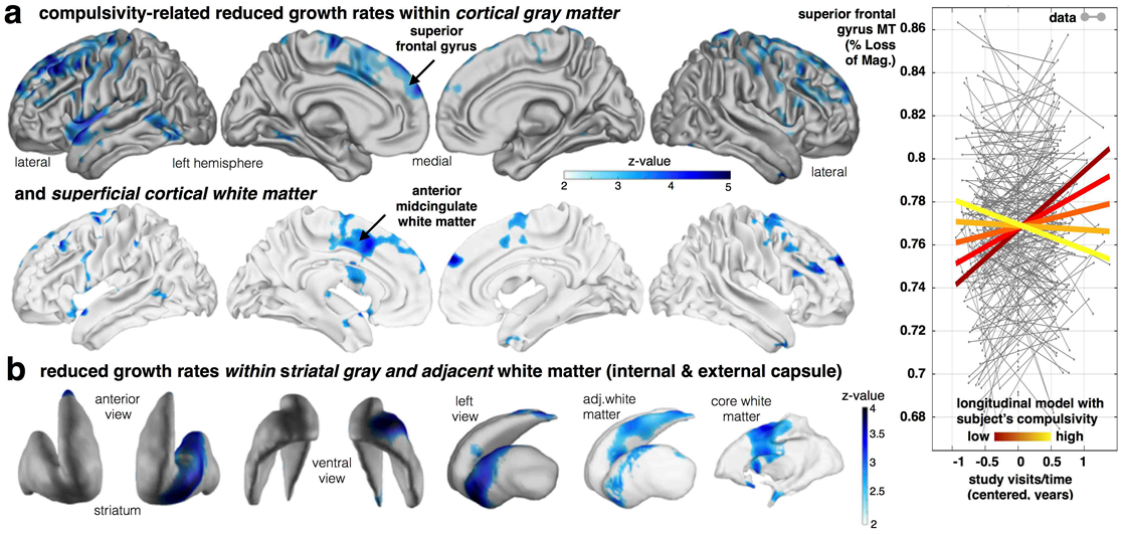

Figure 3. Compulsivity is related to altered fronto-striatal MT growth. Longitudinal developmental change of our myelin marker is reduced in high compulsive subjects. **(a)** Aggregate compulsivity score is related to decreased MT growth in dorsolateral frontal gray matter (upper panel; p<.05, FDR and bootstrapping corrected; Supplementary Table 2) and adjacent white matter, as well as 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.

Reduced inferior prefrontal maturation trajectories in impulsivity

We next examined whether a common heterogeneity in impulsivity (as assessed using the well-established Barratt impulsiveness questionnaire total score; cf Supplementary Fig. 1f) is linked to individual growth of the myelin marker. In examining this linkage we opted to use a questionnaire measure over task-based measures of impulsivity because the former have been found to be more reliable (cf [29–33] for detailed discussion; stability subsample in this study[34] [N=63], BIS total: re-test reliability r=.76 for 1 year follow-up, reflection impulsivity

decision parameter[35]: r=.16 for 6 months follow-up), reflecting a stable trait more likely to be linked to structural development. We found impulsivity was associated with reduction in adolescent MT growth with a strong focus on frontal areas, encompassing lateral (including inferior frontal gyrus, IFG; GM: z=1.65, p=.031 FDR, [-48 13 -4], WM: z=4.38, p=.015 FDR, [-27 39 -2]) and medial prefrontal areas (Fig. 4a, Supplementary Table 3; GM: z=4.13, p=.031, [15 58 18], WM: z=3.69, p=.015, [-12 47 20]), both within gray and adjacent white matter (subcortical effects in Supplementary Fig. 6a).

The above finding suggests that while impulsivity and compulsivity are both linked to reduced myelin-related growth in prefrontal areas, these alterations have their peak expression in distinct anatomical regions (cingulate and dorsolateral vs inferior later and medial prefrontal cortex, for direct comparison cf. Supplementary Fig. 5). Interestingly, both compulsivity and impulsivity showed a reduced growth in the anterior insula (Supplementary Fig. 5), possibly expressing a common, transdiagnostic vulnerability.

We next investigated development-independent levels of myelination in impulsivity, indicating myelin-related differences that emerged before the commencement of our study. This is important because a pre-existing 'hyper-myelination' with the reduced ongoing growth would suggest a normalisation during adolescence, whereas a 'hypo-myelination' prior to adolescence onset would imply that a deficient myelination was further accentuated during adolescence. We found a main effect of impulsivity evident in hypo-myelination across several, primarily anterior prefrontal, brain areas including IFG (Fig. 4c, Supplementary Figure 6b, Supplementary Table 5). An overlap between these baseline effects and areas showing a reduced ongoing growth suggests that for impulsivity a gap in myelination may exist prior to adolescence, with this gap is widening further during a transition into adulthood. The same effects were found when analysing across the entire prefrontal cortex, where a reduced MT growth was linked to both compulsivity (t(421)=1.99,

p<.05) and impulsivity (t(421)=-2.80, p<.05), but where a developmental, baseline hypo-myelination in impulsivity (t(474)=2.30, p<.05) is further accentuated during late adolescent development (no such effect was found for compulsivity: t(427)=1.03, p>.10, Supplementary Figure 7a-b).

Lastly, we examined how MT change related to the development of impulsivity traits. Although we did not see age-related change in impulsivity across the entire group, there was substantial variability within individuals (cf. Supplementary Fig. 1). We thus investigated whether myelin growth in IFG, a key region previously implicated in impulsivity[16], related to ongoing changes in impulsivity. We found that a change in IFG MT was negatively associated with impulsivity change (r=-.27, p<.001, Fig. 4d), indicating that individuals with the least ongoing myelin growth had a worsening impulsivity over the course of the study (irrespective of other covariates, such as baseline impulsivity or age). Similar effects were also seen in prefrontal cortex when using a voxel-wise analysis (cf. Supplementary Figure 7c).

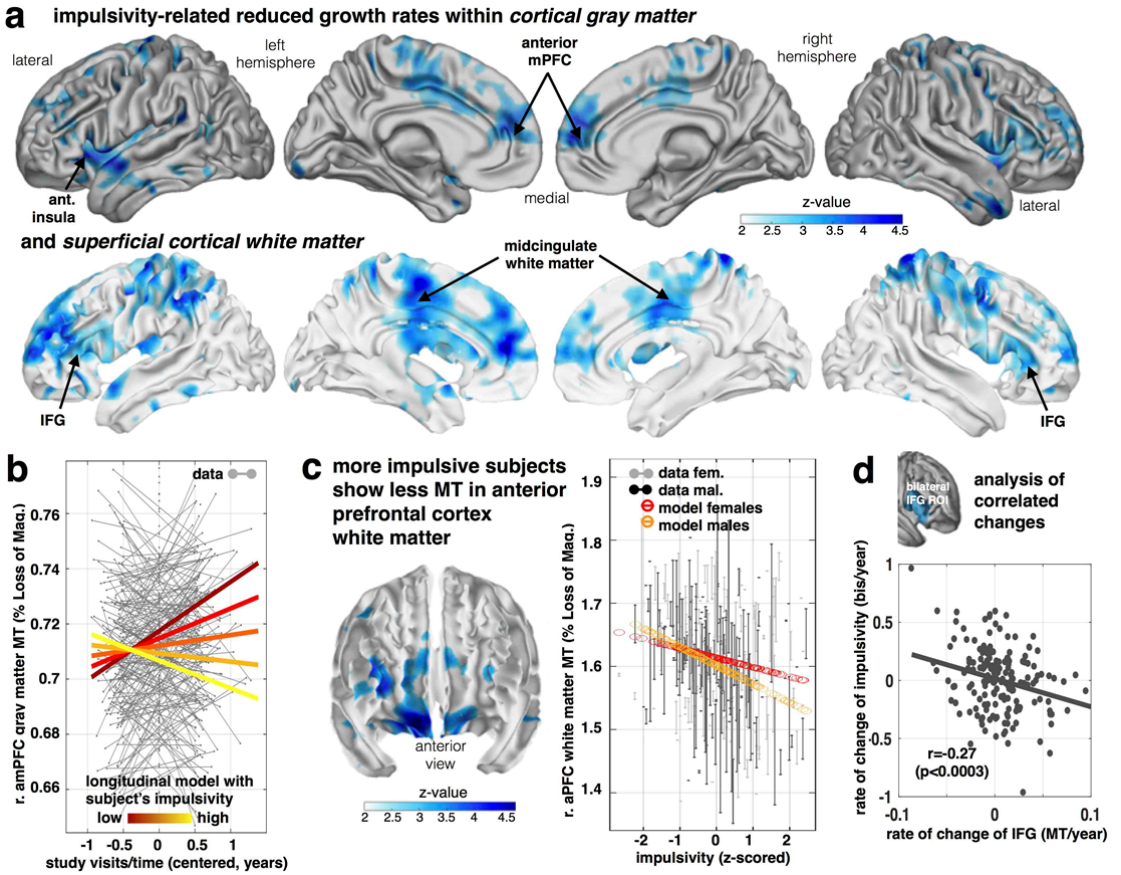

Figure 4. Decreased frontal growth in myelin-sensitive MT in impulsivity. Myelin marker (MT) in frontal lobe is linked to impulsivity traits. **(a)** Impulsivity is associated with reduced growth of MT in lateral (inferior and middle frontal gyrus), medial prefrontal areas, motor/premotor and parietal areas in both gray (top panel) and adjacent white matter (bottom panel) depicting negative time by impulsivity interactions (z maps, p<.05 FDR and bootstrapping corrected, Supplementary Table 3). **(b)** Plot shows 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). **(c)** More impulsive subjects show a local decrement in baseline myelin marker (peak middle frontal gyrus, p<0.05, FDR and bootstrapping corrected, Supplementary Table 5) in lateral and orbitofrontal areas (fixed for other covariates, e.g. time/visits, mean age of subject, sex). 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). **(d)** Bilateral IFG not only shows a reduced myelination process for higher impulsivity (as shown in a, b), but this reduced growth rate is more strongly expressed in subjects who manifest an accentuated impulsivity growth over study visits, such that subjects who manifest an even more restricted growth in myelin become more impulsive.

Discussion

Myelin enables fast and reliable communication within, and between, neuronal populations[36,37]. Using a longitudinal, repeated-measures, MRI scanning design in a developmental sample, we provide *in-vivo* evidence that myelination extends into adulthood as evident in a pronounced myelin-related whole-brain MT growth. We find that the macrostructural growth pattern closely resembles 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, depth-dependent associations suggest that macrostructural volume reduction in adolescence is the result of multiple microstructural processes. In superficial layers, ongoing myelination seems to attenuate the impact of a pruning effect, leading to an apparent slowing in gray matter volume decline. In deeper layers, close to the gray-white matter boundary, ongoing myelination appears to contribute to an inflated estimate of volume reduction, with a myelin-induced 'whitening' of gray matter resulting in a misclassification of gray matter voxels (i.e. partial volume effects[24]), leading to an apparent volume reduction. This observation extends on recent cross-sectional studies that report age-related myelin increases in deep layers[7,25] and implies that developmental neuroimaging that avail of markers sensitive to specific microstructural processes[18] can provide more precise accounts of the likely mechanisms underlying adolescent and early adult brain development.

Critically, we found that individual differences in myelin-related MT growth during development is linked to common heterogeneity in compulsivity and impulsivity within an otherwise healthy sample. Both compulsivity and impulsivity were associated with a reduction in MT growth, and this reduction was almost exclusively present in fronto-striatal areas. In compulsivity, MT growth reduction was primarily expressed in dorsomedial and dorsolateral frontal regions as well as ventral striatum, whereas impulsivity was more tightly

linked to reduction in lateral and medial prefrontal growth. It is worth noting that variability in compulsivity/impulsivity does not reflect clinical impairment in this healthy sample[38]. Our findings extend on previous animal and patient studies that implicate lateral and medial prefrontal regions in attention-related functions[39,40] and ADHD[16,41]. It is also noteworthy that the regions implicated in compulsivity are reported to show altered function in OCD[42,43] and constitute prime targets for invasive OCD treatment interventions[44,45]. Critically, our findings of a reduced myelin unfolding linked to compulsivity suggest that differences in brain structural variables may not prevail during childhood (or only to a minor extent), but emerge during adolescence as a result of aberrant developmental processes.

Embracing a longitudinal developmental approach, as in this study, poses distinct developmental questions. In relation to impulsivity and compulsivity, we can ask how a stable trait is related to longitudinal change as well as baseline myelination differences, where the latter is more indicative of influences emerging prior to recruitment into our study. In the case of impulsivity, we found that ongoing growth occurred in similar regions that also express a difference in baseline myelination, advocating the presence of a pre-existing myelination gap in impulsivity that further expands during adolescence. This suggests that the mechanisms underlying impulsivity have long-lasting effects on brain development, possibly affecting myelination trajectories before adolescence onset with lasting effects into adulthood.

An extension of the approach outlined above poses the question as to how ongoing change in compulsivity and impulsivity relate to ongoing brain maturation (i.e. correlated change). Strikingly, we found that IFG growth change was indicative of change in impulsivity. Subjects who showed worsening of their impulsivity were also those who showed the least maturational myelin-related growth in IFG. Thus, during the transition into early adulthood even though impulsivity traits as a whole do not change at a population level,

individual psychiatric risk trajectories show meaningful variation, and this in turn is reflected in specific patterns of brain maturation.

In our study, we adopted a broad definition of impulsivity and compulsivity traits yet found links to myelin growth. This suggests reduced myelin-related growth in these areas may represent a developmental feature shared across multiple cognitive and/or genetic endophenotypes. This also implies that a more refined cognitive endophenotyping might yield spatially more defined developmental effects[46–48]. Compulsivity and impulsivity showed little overlap in our sample and this relative independence was also reflected in their impact on distinct fronto-striatal brain regions (with the exception of insula which showed a common growth reduction). These data leave open the possibility of a genetic pleiotropy, meaning that a shared genetic factor may drive both myelination and impulsivity/compulsivity, without a direct causal influence between brain and trait expression[49]. However, our correlated change finding that ongoing myelination in the IFG is directly related to how impulsivity evolves over time advocates for the possibility of a direct relationship between myelin-related maturation and impulsivity.

Variability in trait dimensions, such as compulsivity and impulsivity are often related to other variables known to affect brain structure. We examined how potential confounding factors, such as subject movement during scanning (Supplementary Figure 8a-f), alcohol consumption[47,48], recreational drug use, socio-economic status, intelligence (between subject differences and within-subject changes, Supplementary Fig. 9a-c) or ethnicity affected the link between compulsivity/impulsivity and MT growth. Importantly, none of these factors accounted for the observed effects (Supplementary Figure 9d).

A challenge for human neuroscience is to determine the cellular mechanisms that underlie macrostructural change *in-vivo*[50]. This has particular importance for developmental neuroscience where longitudinal, repeated-measures, approaches are critical for

understanding brain development[23]. Our focus in this study on a magnetization transfer (MT) saturation protocol as a proxy for myelin content is rooted in evidence of its sensitivity to myelin and related macromolecules[18], as well as the fact this measure is more robust to instrumental biases[21]. There is also evidence for a strong relationship between MT and myelin as measured in histological studies[19,20,51] and we have shown previously that MT is linked to myelin gene expression[7]. Our longitudinal findings extend the importance of MT as a myelin marker with relevance for individual differences. We show myelin-related effects are expressed in both cortical gray and adjacent white matter, but more pronounced in the former as found also 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 variability in the expression of compulsivity and impulsivity is tied to ongoing microstructural brain development. The brain's potential to dynamically adjust its myelination[52], for example as a function of training[53], points to the potential of interventions that target specific deviant trajectories. 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.

Data Availability Statement

Whole-brain results are available for inspection online on Neurovault (https://neurovault.org/collections/YAHZLJRW/). Data for this specific paper has been uploaded to the Cambridge Data Repository (https://doi.org/10.17863/CAM.12959) and password protected. Our participants did not give informed consent for their measures to be made publicly available, and it is possible that they could be identified from this data set. Access to the data supporting the analyses presented in this paper will be made available to researchers with a reasonable request to openNSPN@medschl.cam.ac.uk or the corresponding authors [G.Z., T.U.H.].

Online Methods

Study design & participants

The NSPN study[34] used an accelerated longitudinal design to investigate variability in compulsivity and impulsivity traits and brain maturation during adolescence and early adulthood. Participants were recruited in London and Cambridgeshire from schools, colleges, primary care services and through advertisement. Subjects were sampled in six age bins 14-15y, 16-17y, 18-19y, 20-21y, and 22-24y, with roughly balanced numbers (overall age mean (std) 19.45 (2.85) years). Each age bin was balanced for sex and ethnicity (relative to the local population). From the 2406 participants that took part in the study and which filled out socio-demographic information and questionnaires at least once, 318 healthy subjects (~60 subjects per age bin) participated in the MRI arm. Subjects with self-reported pervasive neurological, developmental or psychiatric disorders were excluded from the recruitment. We analysed 500 available brain scans from 295 healthy individuals that passed rigorous quality control. In particular, data from 99, 169, and 21 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 analysed psychometric questionnaires that were handed out to the participants over the course of the study. A detailed description of the assessment waves and the overall structure of the NSPN study is provided elsewhere[34]. As an index of impulsivity, we used the Barratt Impulsiveness Scale (BIS)[48] total score, a well-established and calibrated measure of general impulsivity. To assess compulsivity, we built a composite score (using principal component

analysis (PCA), cf supplementary information) from two established obsessive-compulsive questionnaires that were available in this study (Supplementary Fig. 1a-e, revised Obsessive-Compulsive Inventory, OCI-R[27], and revised Padua Inventory, PI-WSUR[26]).

Questionnaires were assessed at several times throughout the study. BIS was completed at home by participants on up to three occasions (ca 1 year between assessments), with the first assessment wave taking place before initial scanning. PI-WSUR was also completed at home during waves 2 and 3. OCI-R was assessed on the day of the second MRI scan. Per construction, the considered psychometric questionnaires aim at measuring stable subject-specific traits but cognitive constructs could as well change over the course of this longitudinal study. In our sample, linear mixed-effects modelling (LME, cf supplementary information) revealed that both indices did not substantially change during the study period while accounting for covariates and confounds, which motivated our use of aggregated scores (LME intercepts) for most of the subsequent MRI analyses on impulsivity. Compulsivity and impulsivity trait measures showed a weak correlation r=0.119 in the large behavioural sample, supporting a notion of rather independent dimensions (less than 1.4% shared variance, cf Supplementary Fig. 1).

MRI data acquisition and longitudinal preprocessing

Brain scans were acquired using the multi-echo FLASH MPM protocol[55] on three 3T Siemens Magnetom TIM Trio MRI systems located in Cambridge and London. Comparability between scanners was assessed prior to study onset (for more details, cf [34]) and differences between scanners were accounted for by adding scanner as covariates in our analyses. Isotropic 1mm MT maps were collected to quantify local changes in gray and adjacent white matter and all image processing was performed using SPM12 (Wellcome Centre for Human Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm), the h-MRI

toolbox for SPM[56,57] (www.hmri.info), Computational Anatomy toolbox (CAT, http://www.neuro.uni-jena.de/cat/) and custom made tools (cf code availability statement).

Magnetization transfer saturation (MT) maps provide semi-quantitative maps for myelin and related macro-molecules, and correlate highly with myelin content in histological studies[19,20]. MT shows a high sensitivity to actual microstructural changes such as myelin and thus overcomes limitations in previous methods, such as diffusion tensor imaging, which measure microstructural change only indirectly through assessing diffusivity[58]. It was also found to be more robust than earlier protocols such as magnetization transfer ratio[21]. This is important also because myelin patterns are defining for brain anatomy and are used for subdividing brain structures[59,60].

Since longitudinal neuroimaging is prone to artefacts due to registration inconsistency, scanner inconsistencies and age-related deformations of the brains, we developed advanced processing pipelines in order to detect the changes of interest and achieve unbiased results. To assess the microstructural myelin-related MT changes during development, we used a longitudinal processing pipeline with the following steps (Supplementary Fig. 2a). To normalise images, we performed a symmetric diffeomorphic registration for longitudinal MRI[61]. The optimization is realized within one integrated generative model and provides consistent estimates of within-subject brain deformations over the study period and a midpoint image for each subject. The midpoint image is subsequently segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid using CAT. MT maps from all time-points were then normalized to MNI space using geodesic shooting[62,63], spatially smoothed preserving GM/WM tissue boundaries[57], and manually as well as statistically quality checked using a proxy for during-scan motion (cf. Supplementary Fig. 8) and covariance-based sample homogeneity measures (as implemented in CAT).

Lastly, we constructed masks for both gray and adjacent white matter using anatomical atlases for subsequent analysis (cf. illustrated in Supplementary Fig. 2b).

To relate these quantitative (Voxel-Based Quantification, VBQ) to more conventional metrics (i.e. Voxel-Based Morphometry), we normalized tissue segment maps to account for existing differences and ongoing changes of local volumes using within- and between-subjects modulation. The obtained maps were spatially smoothed (6 mm FWHM). All analyses were conducted in voxel-space, and then projected onto surface space for illustration purposes. Voxel-wise result maps can be inspected online (cf data availability statement).

In this paper, we focused on the developmental VBQ analysis of myelin-sensitive MT. Since this is the first longitudinal study with this marker, effects of demographics (time/visits, age and sex) as well as impulsivity and compulsivity were considered on the whole-brain level. The analyses were particularly aimed at exploring MT in gray matter and the adjacent superficial white matter tissue. In order to define disjunct but adjacent gray and white matter regions for voxel-based analysis in the MNI template space, the gray and white matter tissue classes of the template were thresholded with 0.5, resulting in an approximately symmetric GM/WM boundary, i.e. with roughly 0.5 probability for each tissue class for voxels on the boundary (shown in Fig. 2). The resulting (non-overlapping) canonical gray and white matter tissue masks are not expected to be biased towards either gray or white matter and thus avoid over- or underestimation on both tissue classes. The subcortical gray and white matter masks were computed analogously.

Longitudinal design specification and MT image analyses

In this study, we employed a longitudinal observational design to examine 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[64], such as cohort differences[65,66] or selection bias[67], 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 of time or (b) all subjects change in the same way. Here, we follow recent analysis recommendations[68], 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/visits (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)[68] method for voxel-based longitudinal image analysis (http://www.nisox.org/Software/SwE; cf supplementary information). Similar to common cross-sectional general linear modelling (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 (illustrated in Supplementary Fig. 2b),

In our developmental analyses, we focused on the factors time/visits and mean age of the individual (over all visits). Moreover, in order to investigate if, and how, compulsivity and impulsivity traits are related to brain trajectories and altered growth we enriched the models by adding a main effect of trait (compulsivity/impulsivity), as well as their interaction with change over time/visits. The latter metric allowed us to assess how MT growth is associated with compulsivity and impulsivity traits (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 specifically mentioned, all analyses were performed in a dimensional manner using the subjects' trait scores directly rather than comparing median-split groups. Notably, in addition to including effects time/visit, mean age of subject (further denoted

age_mean), and compulsivity/impulsivity traits, all models were tested for indications of effects of (a) other relevant demographic factors, especially sex and socioeconomic status (as measured by national poverty index[69]); (b) effects of during scan motion as indicated by standard deviation of R2* exponential decay residuals in white matter areas (cf. supplementary methods and Supplementary Fig. 8a-c); (c) non-linearites (accelerations/deceleration) of brain changes (across the study age range) and age-related trajectories, especially using time by age_mean interactions, and quadratic/cubic effects of age_mean; and (d) all first order interactions among all previous covariates. More detailed notes on longitudinal modelling and design specification can be found in supplementary information.

There were no indications of substantial non-linearities for myelin-sensitive MT (cf Supplementary Fig. 3d), but for volumes (cf Supplementary Fig. 4b). Demographic covariates and confounds (motion, 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 during morphometric analysis. Additionally, this allows utilisation of a consistent design (and power) across modalities. We additionally examined the effects of potentially confounding covariates, such as alcohol consumption, recreational drug use, ethnicity ('white' vs 'other'), and IQ, but did not find any effect on our main results (cf. Supplementary Fig. 9d). We controlled for the False Discovery Rate (FDR) during corrections for multiple comparisons in all image analyses. We additionally report bootstrapping-based results (cf. Supplementary Fig. 2c; Supplementary Tables 1-3 & 5).

To examine the topographical similarity of growth effects in gray and adjacent white matter, we assessed the correlation between GM and nearest neighbouring WM voxels (significance tested using 1000 permutation tests).

Analysis of macrostructural changes and MT/Volume associations

To relate the findings from our microstructural myelin marker (MT) to traditional macrostructural markers (GM/WM volume), we performed analogue analyses (using VBM[70]) 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 (block-diagonal) 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 covariates[71]. Random-effect intercepts were included and proved optimally suited using likelihood ratio tests. Global frontal MT was analysed separately for each dimension (shown in Supplementary Fig. 7a) and jointly with both dimensions (and their interaction) included in the design (Supplementary Fig. 7b). For

both of these global models, we used discrete (median split bivariate traits: low vs. high) for simplified illustration although continuous variables were used during modelling.

Analysis of correlated changes of brain and impulsivity

To assess whether MT development was related individual changes in impulsivity, we conducted a hypothesis-driven analysis of the bilateral IGF (anatomically defined). This LME analysis provides information about whether changes in impulsivity also reflect how quickly a brain region myelinates during the study period. The LME model used IFG MT, rates of change in IFG MT, time, their interaction, as well as the above introduced covariates as fixed effect to predict the dependent variable impulsivity score. We visualize the observed correlated changes using simple correlations. In addition, we conducted exploratory voxel-wise correlated change analyses. Time-varying BIS scores were decomposed in purely within- and between-subject components and entered as regressors in voxel-wise SwE modelling of myelin-sensitive MT (in addition to covariates *time/visits, age_mean, sex, interactions and confounds*, cf. supplemental information).

Analysis of MT peak effect specificity for both traits and compulsivity subtests

Above described voxel-based SwE analysis assessed whether there is region-specific growth in myelin-sensitive MT and compulsivity and impulsivity related impairment of the ongoing myelination process. However, here we complemented this by a subsequent analysis of MT in observed fronto-striatal peak effects (Fig. 3 and 4) and global frontal MT using LME modelling. More specifically, we were interested in specificity of local brain trajectories associated with each or eventually both impulsivity and compulsivity *traits*. The fixed effects design was specified with X = *[intercept, time/visit, time by trait interaction,*

trait, age_mean, sex, socioeconomic status, confounders] (similar to the mass-univariate SwE models above). We explored the potential interaction of both dimensions, in addition to the separate modelling (presented in Fig. 3 & 4) a joint model was specified including both *traits* simultaneously, as well as their interaction (not found to be significant), and their respective interactions with *time/visits.* By inclusion of both effects of *trait* as well as their *time by trait interaction*, we accounted for potential baseline and rate-of-change differences related to both trait dimensions simultaneously rendering coefficients/statistics specific for each dimension. Random effects were restricted to intercepts. The specificity of MT (averaged in 6mm sphere around peaks observed in voxel-based SwE analysis above) for compulsivity and impulsivity is presented in Supplementary Fig. 5. Finally, we assessed the specificity of two available compulsivity scores, OCI-R and PI-WSUR for the observed reduced MT growth effects using our compulsivity dimension (from PCA). Thus, we explored each subscore's main effect and time/visit interactions on local MT trajectories (in averaged in 6mm spheres of peaks presented in Fig. 3a) as detailed in Supplementary Fig. 6c.

Code availability

Custom made SPM pipeline code for longitudinal VBM and VBQ processing is provided along with the manuscript (https://github.com/gabrielziegler/gz/tree/master/nspn_mpm_prepro_code_and_example). The code aims at transparency of applied procedures but is not intended for clinical use. It is free but copyright software, distributed under the terms of the GNU General Public Licence as published by the Free Software Foundation (either version 2, or at your option, any later version). For any questions and requests please contact gabriel.ziegler@dzne.de

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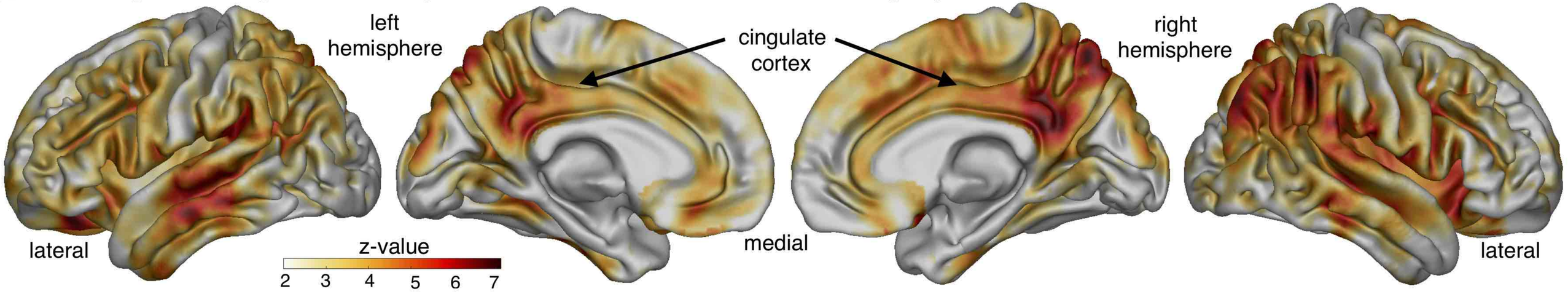
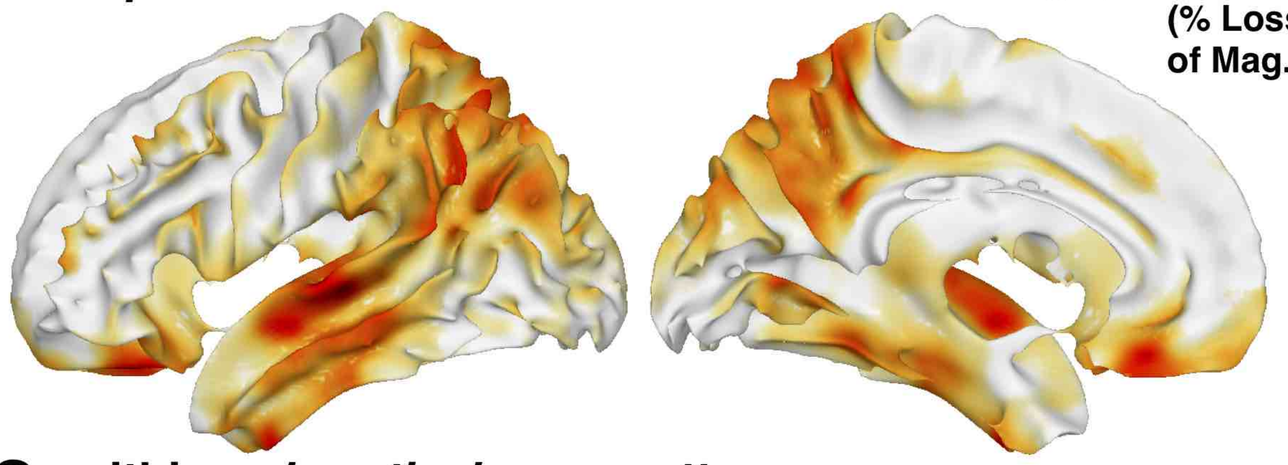
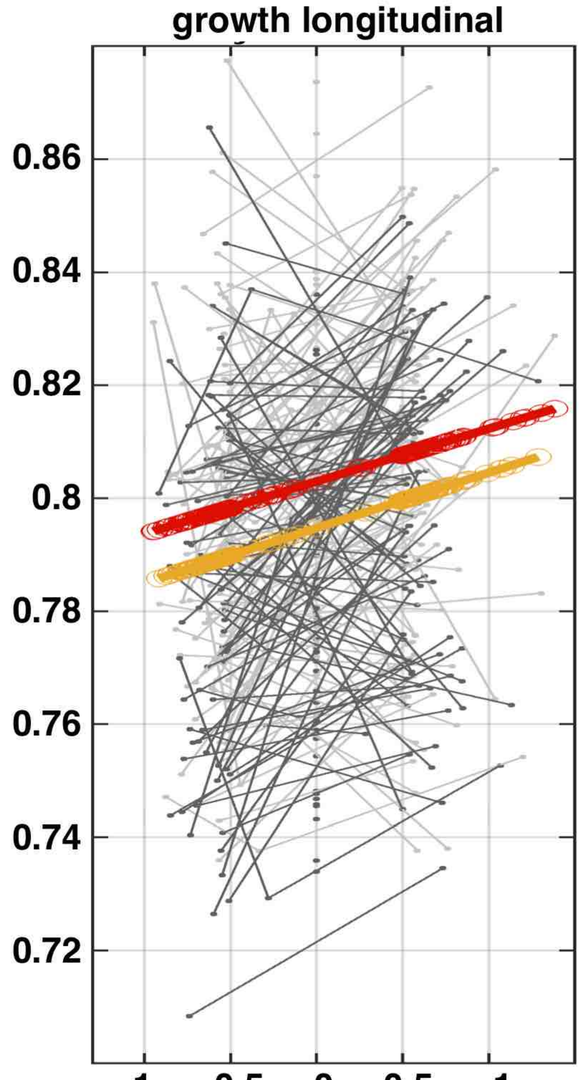
a **developmental growth of myelin-sensitive MT within c*ortical gray matter***

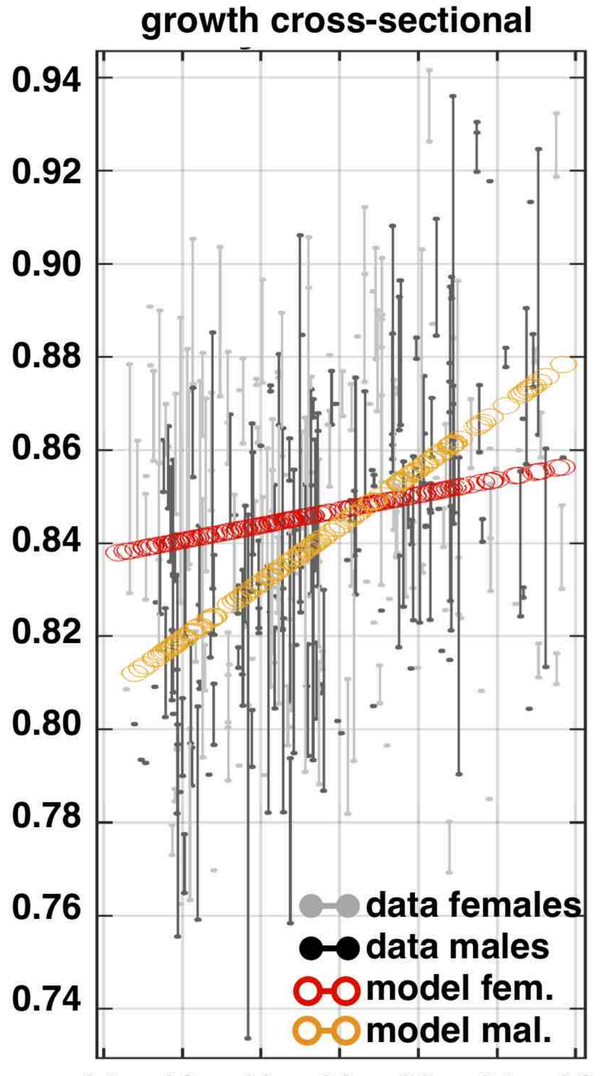


b **growth of MT in adjacent *superficial cortical white matter***

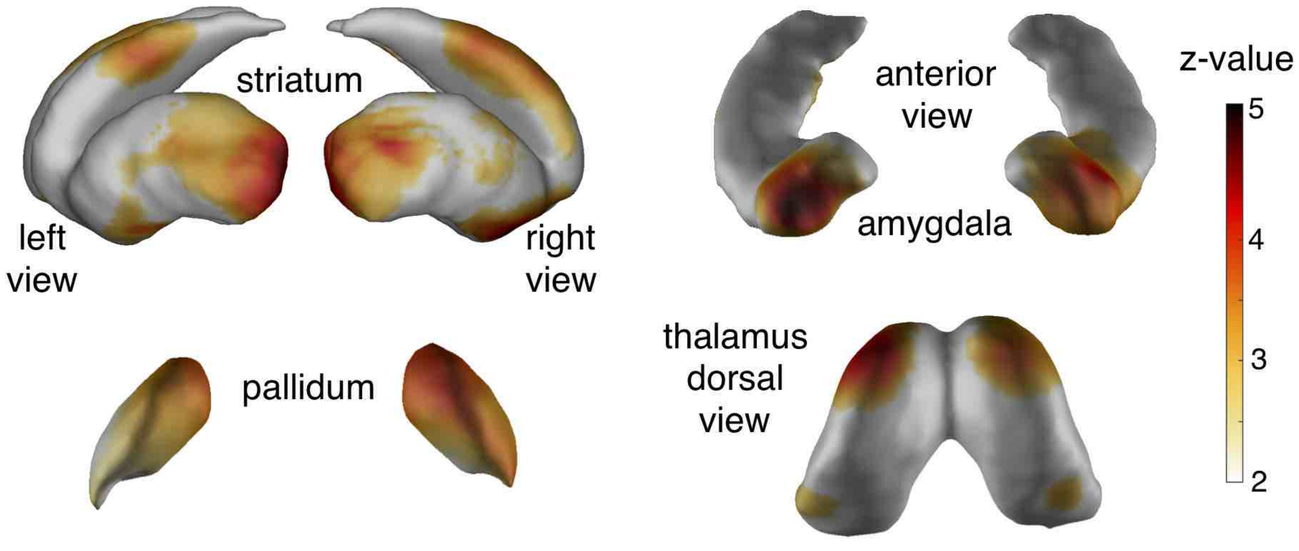


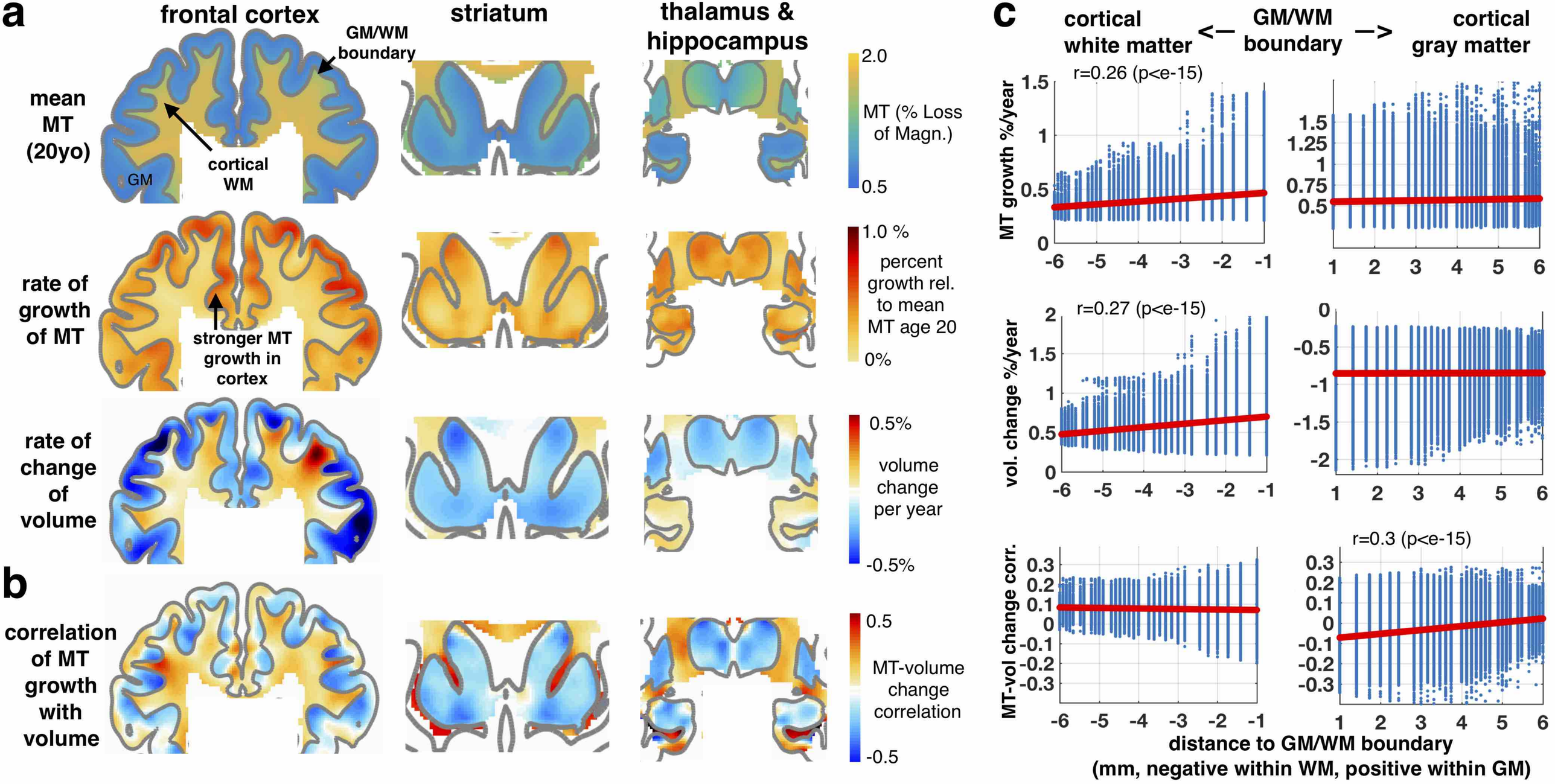
r. angular gyrus gray matter MT (% Loss of Mag.)

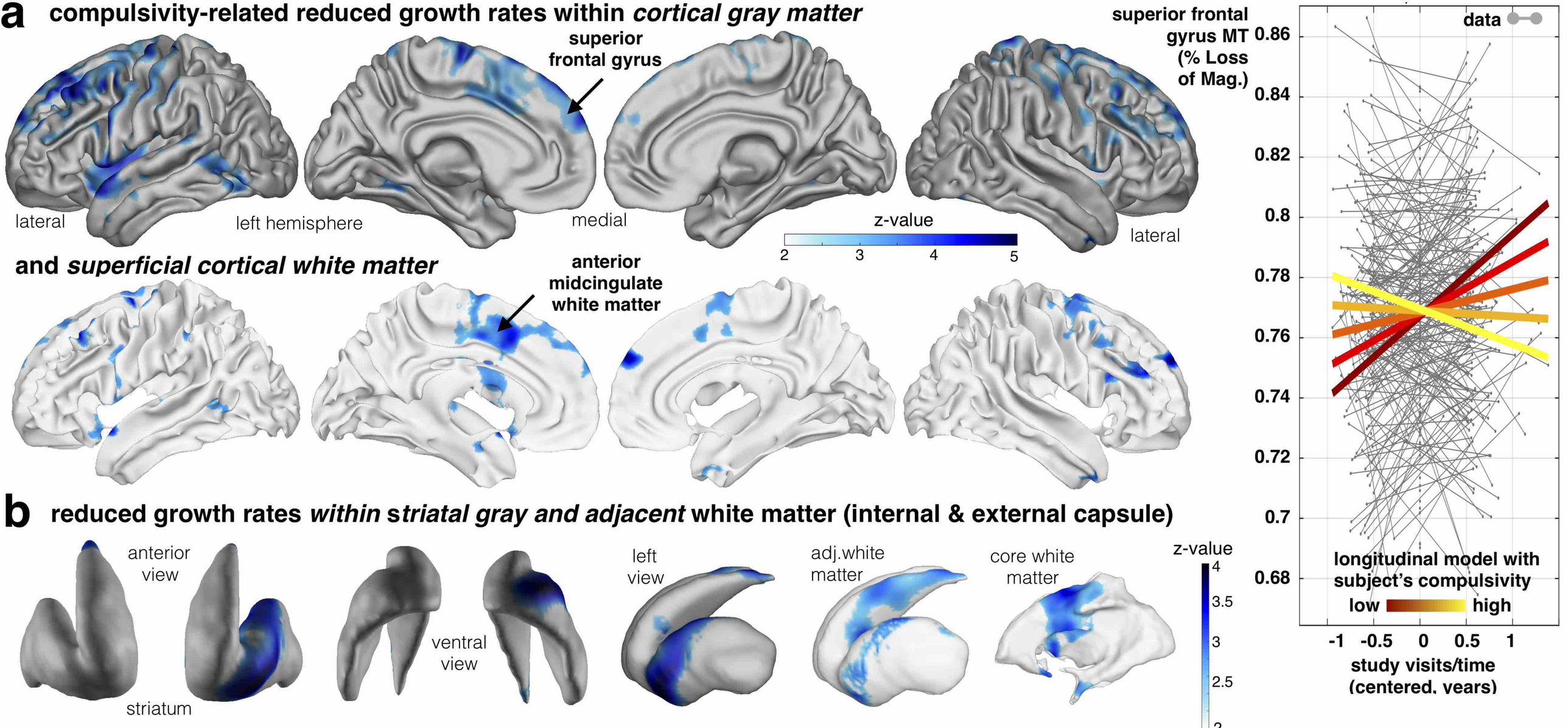




c **within *subcortical gray matter***




a
frontal cortex
striatum
thalamus & hippocampus
GM/WM boundary
mean MT (20yo)
GM
cortical WM
rate of growth of MT
stronger MT growth in cortex
rate of change of volume
b
correlation of MT growth with volume
2.0
MT (% Loss of Magn.)
0.5
1.0 %
percent growth rel. to mean MT age 20
0%
0.5%
volume change per year
-0.5%
0.5
MT-volume change correlation
-0.5
c
cortical white matter
<—
GM/WM boundary
—>
cortical gray matter
r=0.26 (p<e-15)
MT growth %/year
r=0.27 (p<e-15)
vol. change %/year
r=0.3 (p<e-15)
MT-vol change corr.
distance to GM/WM boundary
(mm, negative within WM, positive within GM)


a
compulsivity-related reduced growth rates within cortical gray matter
superior frontal gyrus
lateral
left hemisphere
medial
lateral
z-value
2
3
4
5
and superficial cortical white matter
anterior midcingulate white matter
b
reduced growth rates within striatal gray and adjacent white matter (internal & external capsule)
anterior view
striatum
ventral view
left view
adj.white matter
core white matter
z-value
4
3.5
3
2.5
superior frontal gyrus MT (% Loss of Mag.)
0.86
0.84
0.82
0.8
0.78
0.76
0.74
0.72
0.7
0.68
data
longitudinal model with subject's compulsivity
low
high
-1
-0.5
0
0.5
1
study visits/time (centered, years)

a **impulsivity-related reduced growth rates within *cortical gray matter***

lateral

left hemisphere

anterior mPFC

right hemisphere

ant. insula

medial

lateral

z-value

2 2.5 3 3.5 4 4.5

and *superficial cortical white matter*

midcingulate white matter

IFG

IFG

b

data

r. amPFC grav matter MT (% Loss of Maq.)

0.76 0.74 0.72 0.7 0.68 0.66

longitudinal model with subject's impulsivity

low high

-1 -0.5 0 0.5 1

study visits/time (centered, years)

c **more impulsive subjects show less MT in anterior prefrontal cortex white matter**

anterior view

z-value

2 2.5 3 3.5 4 4.5

data fem.

data mal.

model females

model males

r. aPFC white matter MT (% Loss of Maq.)

1.9 1.8 1.7 1.6 1.5 1.4

-2 -1 0 1 2

impulsivity (z-scored)

d

bilateral IFG ROI

analysis of correlated changes

rate of change of impulsivity (bis/year)

1 0.5 0 -0.5 -1

r=-0.27

(p<0.0003)

-0.1 0 0.1

rate of change of IFG (MT/year)