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Longitudinal associations between adolescent catch-up sleep, white-matter maturation and internalizing problems[☆]

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ABSTRACT

Sleep is an important contributor for neural maturation and emotion regulation during adolescence, with long-term effects on a range of white matter tracts implicated in affective processing in at-risk populations. We investigated the effects of adolescent sleep patterns on longitudinal changes in white matter development and whether this is related to the emergence of emotional (internalizing) problems. Sleep patterns and internalizing problems were assessed using self-report questionnaires in adolescents recruited in the general population

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White Matter
DTI
MRI
Internalized symptoms
Anxiety
Depression
Prevention
Longitudinal
Cohort
Adolescents

followed up from age 14–19 years ($N = 111$ White matter structure was measured using diffusion tensor imaging (DTI) and estimated using fractional anisotropy (FA). We found that longitudinal increases in time in bed (TIB) on weekends and increases in TIB-variability between weekdays to weekend, were associated with an increase in FA in various interhemispheric and cortico-striatal tracts. Extracted FA values from left superior longitudinal fasciculus mediated the relationship between increases in TIB on weekends and a decrease in internalizing problems. These results imply that while insufficient sleep might have potentially harmful effects on long-term white matter development and internalizing problems, longer sleep duration on weekends (catch-up sleep) might be a natural counteractive and protective strategy.

1. Introduction

Sleep behaviours undergo characteristic changes during adolescence (Colrain and Baker, 2011; Crowley et al., 2007; Dahl and Lewin, 2002; Tarokh et al., 2016), including a decrease in sleep duration with age (National Sleep Foundation, 2006), later sleep times and a greater sleep duration variability on a day-to-day and weekday-to-weekend basis (Dahl and Lewin, 2002). Reduced sleep duration is commonly the results of a mismatch between internally and externally regulated factors, which include later bed times and increasingly early or constant wake-up times (e.g. work or school schedules; Cain and Gradisar, 2010; Carskadon, Vieira, and Acebo, 1993; Carter, Rees, Hale, Bhattacharjee, and Paradkar, 2016; Jenni, Achermann, and Carskadon, 2005; Owens and Adolescent Sleep Working Group, 2014). Consequently, adolescents often accumulate a sleep deficit during weeknights, which they aim to compensate with a longer sleep duration on weekends (Crowley et al., 2007; Owens and Adolescent Sleep Working Group, 2014; Roberts et al., 2009; National Sleep Foundation, 2006). Such catch-up sleep is often marked by a sleep duration variability from weekday to weekend of approx. 2 h (Owens and Adolescent Sleep Working Group, 2014; National Sleep Foundation, 2006).

These characteristic sleep changes are problematic, since sleep problems, particularly sleep curtailment, have been suggested to relate with the onset of emotional problems, including internalizing problems (negative behaviours and emotions directed inwards), such as depressive symptoms, anxiety, suicidal ideation and dysfunctional emotion regulation (Carli et al., 2014; Gregory et al., 2005; Gregory and O'Connor, 2002; Owens and Adolescent Sleep Working Group, 2014; Roberts et al., 2009). Both long-term (Baum et al., 2014) and short-term (Short and Louca, 2015; Talbot et al., 2010) sleep restriction lead to a decrease in positive affect, an increase in anxiety levels and impede emotion regulation in healthy adolescents. Meta-analytic evidence shows that restricted sleep duration in particular, relates with internalizing problems in 5–12 year old children (Astill et al., 2012) and persistent sleep problems in childhood predict internalizing problems in adolescence (Gregory and O'Connor, 2002) and adulthood (Gregory et al., 2005). In contrast, a short sleep onset latency and high sleep efficiency, are predictive of resilience to depression (Silk et al., 2007). More generally, a longer sleep duration can have positive benefits on emotion regulation, alertness and impulse control in children (Gruber et al., 2012) and better sleep quality can lead to improvements in depression and anxiety (Scott et al., 2021).

Sleep habits are also associated with organization and function of the developing brain (Tarokh et al., 2016). Previous work has shown that sleep habits are associated with the neural structure in local grey (Taki et al., 2012; Urrila et al., 2017) and white matter (Jamieson et al., 2020, 2021; Telzer et al., 2015). White matter circuits undergo prolonged maturation in adolescence and, hence, remain particularly vulnerable to maladaptive influences (Asato et al., 2010; Giorgio et al., 2010). Fibre tract coherence and integrity as well as myelination continue to increase with age across many projection and association tracts (Bava et al., 2010; Giorgio et al., 2010; Lebel and Beaulieu, 2011). Sleep functions as a promoter of such neurobiological maturation processes (Jan et al., 2010) and insufficient and irregular sleep patterns may have long-term

counteractive effects on normative white-matter trajectories in developing tracts (Jamieson et al., 2021; Telzer et al., 2015).

Disturbances in white matter tracts are associated with a number of affective symptoms (Thomason and Thompson, 2011). Depression has been related with impaired connectivity between the prefrontal cortex (PFC) and cortical, as well as subcortical structures leading to a lack of regulatory modulation in the processing of negative affective information and general cognitive processing (Liao et al., 2013; Price and Drevets, 2010). Altered structure and function in these circuits were reported in treatment naïve adolescents with first episode major depression (Geng et al., 2016). Specifically, microstructural changes in white matter tracts, such as the superior longitudinal fasciculus (SLF), the uncinate fasciculus (UF), or corpus callosum, were associated with adolescent depression (Aghajani et al., 2014; Lewinn et al., 2014; but see van Velzen et al., 2020, for a recent large-scale meta-analysis reporting no difference in FA in adolescents with clinical depression) and dysregulation of emotions (Versace et al., 2015). However, reduced fractional anisotropy (FA) in the above-mentioned white matter circuits has thus been suggested to denote a risk factor in the development of affective disorders (Lewinn et al., 2014). Accordingly, adolescents at high risk for developing a depressive disorder show characteristic decreases in FA in the SLF, corpus callosum, UF and inferior fronto-occipital fasciculus (IFOF; Huang, Fan, Williamson, and Rao, 2011). However, meta-analytic evidence suggests that the most stable finding refers to the left SLF, where FA reduction was moreover associated with symptom severity (Murphy and Frodl, 2011).

Although increasing efforts have been directed at delineating the relationship between sleep and psychopathology in adolescence, little work has directly explored longitudinal interactions between aspects of sleep, brain maturation and internalizing problems. Although sleep and emotional well-being undoubtedly interact in a bi-directional manner (Gregory and Sadeh, 2012), the focus of this study lay on the possible risks associated with adolescent sleep behaviour on emotional well-being. As outlined above, maladaptive sleep patterns might impact emotional well-being by impeding brain maturation processes during sleep. Therefore, we tested whether change in white matter development might be a factor through which insufficient sleep impacts psychological well-being. Specifically, we tested the association of sleep and white matter microstructure, and whether the white matter microstructure mediates the changes in internalizing symptoms in adolescence. Based on previous literature (Telzer et al., 2015), we expected that between the ages 14–19, (i) a longitudinal decrease in sleep duration (time-in-bed) and increase in weekday to weekend time-in-bed variability (catch-up sleep), would be associated with longitudinal changes in FA. We hypothesized that the implicated tracts would be part of cortico-striatal, cortico-cortical as well as thalamo-cortical circuits, such as the SLF, IFOF and the corpus callosum. We furthermore hypothesized that (ii) changes in FA in tracts associated with sleep would mediate the change in magnitude of internalizing problems from early to late adolescence, based on the association between depressive symptoms and FA changes, particularly in SLF (Murphy and Frodl, 2011). We also explored the association in other tracts including IFOF, corpus callosum and uncinate fasciculus, given that they were associated with sleep and have been previously associated with affective problems in

adolescence (Aghajani et al., 2014; Huang et al., 2011; Lewinn et al., 2014).

2. Materials and methods

2.1. Participants

The French subset of the IMAGEN European cohort was examined and assessed for sleep behaviour. Based on their age, participants without a major somatic, neurological, or psychiatric conditions (for detailed description see (Schumann et al., 2010) were recruited from the general population in the south Paris area. The participants underwent DTI scans at two time points ($M_{\text{baseline}} = 14.5$ yrs, $SD = .44$; $M_{\text{follow-up}} = 19.8$ yrs, $SD = .62$) over a period of approx. 5 years (± 7 months). At both measurements, $N = 145$ participants filled out a number of psychological instruments concerning their sleep behaviour and emotional problems. Thirty-one participants were excluded from the analysis, because they neither had DTI nor passed DTI quality control at both or either of the two time points (see DTI acquisition and preprocessing for details). An additional 3 subjects were excluded because of a considerable increase in drug consumption between the time points (increase in the alcohol use disorder identification test; AUDIT (Saunders et al., 1993) points over 15. The AUDIT is a well-established and internationally used screening instrument to evaluate hazardous to clinically relevant alcohol consumption on 10 items. Scores can range from 0 to 40 and indicate reflect the amount and frequency of drinking alcohol. Data from the remaining $N = 111$ adolescents (59 females) is presented in the current work. Participants and their parents had given their informed consent prior to participation in accordance with the declaration of Helsinki (1991; p. 1194). The study was approved by the Parisian Ethics Committee, CPP IDF-VII.

2.2. Sleep assessment

To obtain a subjective measure of sleep schedule the participants reported their retire times (e.g. “When do you usually go to bed on a weekday?”) and their wake-up times (e.g. “When do you usually wake-up on a weekday?”), on weekdays and on weekends at both time points. *Retire- and wake up- variability* indicate the difference in reported times between weekdays and weekends. From the retire and wake-up times, we calculated the participants’ *time spent in bed (TIB) during weekdays* and *time spent in bed (TIB) during weekends*, as the difference between reported retire times and wake-up times. *TIB-variability* was calculated by subtracting weekday from weekend TIB. Longitudinal changes in these variables are henceforth denoted by a Δ (calculated by subtracting baseline from follow-up measures). Thus, Δ *TIB-variability* refers to the 5-year change in difference between time spent in bed (TIB) on weeknights and weekends in minutes, and accordingly, Δ *TIB weekend* refers to the 5-year change in time spent in bed (TIB) on weekends in minutes.

2.3. Assessment of internalizing symptoms

The French version of the Strength and Difficulties Questionnaire (SDQ; Goodman, 1997) was employed to assess internalizing problems at both time points. The 25-item SDQ includes five subscales assessing emotional symptoms, conduct problems, hyperactivity, peer problems, and pro-social behaviour. Internalizing problems are calculated as the sum score of the subscales emotional symptoms (e.g. “I have many fears, I am easily scared”, “I am often unhappy, down-hearted or tearful”) and peer difficulties (e.g. “I am usually on my own. I generally play alone or keep to myself”, “Other Children or young people pick on me or bully me”). The internalizing scale shows good construct validity in community samples and is recommended as a proxy of emotional problems directed inward (A. Goodman et al., 2010; Niclasen et al., 2013).

2.4. DTI acquisition and preprocessing

Diffusion tensor images were acquired at time point one and two with 3 Tesla Siemens Trio MRI scanners in two different sites. We accounted for variation caused by two Trio MRI scanners by introducing a confounding dummy variable during the statistical analysis. The diffusion tensor images were acquired using an Echo-planar imaging (EPI) sequence (4 times $b = 0$ s/mm² and 32 diffusion encoding directions with $b = 1300$ s/mm²; 60 oblique-axial slices (angulated parallel to the AC/PC line); echo time ≈ 104 ms; 128×128 matrix; field of view $307 \text{ mm} \times 307 \text{ mm}$; voxel size $2.4 \text{ mm} \times 2.4 \text{ mm} \times 2.4 \text{ mm}$). Where available, a peripherally gated sequence was used; when this was not possible, TR was set to 15 s, approximately matching the effective TR of the gated scans.

Acquired data were first pre-processed using the FMRIB Diffusion Toolbox in the FSL software (www.fmrib.ox.ac.uk/fsl; Smith et al., 2004). Affine registration to the first $b = 0$ image was conducted to correct for head motion and eddy currents (using “eddy_correct”). The Brain Extraction Tool (BET) was used to exclude non-brain signals. Diffusion tensors were estimated and Fractional Anisotropy (FA) computed for each voxel. Exclusion criteria were defined based on the number of volumes ($n = 36$) and slices ($n = 60$) (exclusion if not 36 and 60), slice by slice for divergent values indicating a signal dropout (exclusion if number of slices > 10), volume by volume for head rotation based on the matrix used for the affine registration (exclusion if number of volumes with 5° rotation > 1), the tensor computation by using a k-means clustering on the global FA, MD, L1, L2, L3 and MO values (exclusion if not in the main cluster). Twenty-five participants were excluded as they did not have DTI sequence. Quality control on the raw DTI images was performed automatically on signal dropouts, head motion and tensor fitting computation. Two subjects were excluded due to signal dropout (more than 10 slices) or head motion (more than 5° rotation). Two subjects were excluded by K-means clustering due to poor tensor fitting. Quality control on the imaging preprocessing was performed visually on the masking and the spatial normalization. Two subjects were excluded due to poor brain extraction or spatial registration (see Supplementary Fig. S1).

Fractional anisotropy values range from 0 (isotropic) to 1 (anisotropic diffusion) and indicate the net directionality of water diffusion in the given tissue (Pierpaoli and Basser, 1996). The TBSS (tract based spatial statistics; Smith et al., 2006) toolbox in FSL was used to compute voxel wise across subject statistical analysis of FA data. Following the recommendation for TBSS analyses (Bach et al., 2014), we used a tensor-based registration (DTI-TK; Zhang, Yushkevich, Alexander, and Gee, 2006) to align all individuals into a common space. Next, the mean FA image was created and thinned to create a mean FA skeleton which represents the centres of all tracts common to the group. This skeleton was thresholded to $FA > .02$ to keep only the main tracts. Each subject’s aligned FA data was then projected onto this skeleton.

2.5. Statistical analyses

Data management and analyses of global variables were conducted using R (<http://www.r-project.org/>). All variables were assessed regarding outliers, errors in data entry and missing values. All statistics involving DTI were corrected for multiple comparisons. The longitudinal effect of age on the mean FA skeleton was estimated in the framework of linear mixed effects models, allowing us to model a random intercept for each subject and including time as predictor variable and gender, as well as alcohol consumption (AUDIT scores) as covariates. Likelihood ratio tests were performed to test the effect of age on FA development, by comparing the models with fixed effects to the null models with only the random intercepts using the χ^2 statistic.

For the longitudinal voxel-wise analysis, individual FA skeleton difference between time point 1 and point 2 were computed. To test the effect of sleep on FA development, data were entered into regression

models using a standard GLM design in FSL statistical toolbox and 5000 permutations. For each sleep variable, the sleep measure change (Δ) was entered as variable of interest and sleep measure at baseline, age at baseline, time interval, gender and change in alcohol consumption (Δ AUDIT) as confounding variables. To check for systematic variation caused by two Siemens Trio MRI scanners, we ran extra analyses with MRI type as an additional covariate, which had no effect on the results and was excluded from the model. The voxel-wise statistical threshold was set at $p < .05$, corrected for multiple comparisons with family-wise error correction (FWE) and Threshold-Free Cluster enhancement (TFCE). Tracts that contained significant correlations with sleep indices were identified based on the JHU ICBM-DTI-81 White Matter Labels and the JHU White-Matter Tractography atlas.

Partial Pearson correlation coefficients were calculated to assess the association between Δ internalizing problems and the sleep variables. We controlled for age at baseline, time interval and gender. Finally, to assess whether the change in FA in the relevant tracts as a function of sleep variables mediates the occurrence of internalizing problems, we performed causal mediation analyses. This allows to dissociate the total, direct and mediation effects within the framework of general linear models (Imai et al., 2010). The longitudinal sleep variables (Δ) were entered as independent variables predicting the Δ internalizing scores, with extracted FA values in significant clusters identified by the TBSS analysis in left SLF, IFOF, corpus callosum and uncinate accordingly as mediators and age at baseline, time interval, gender and alcohol consumption (Δ AUDIT) as covariates of no interest. FA values in significant clusters were extracted by masking the FA difference skeleton using the JHU atlases. 5000 Monte Carlo draws for non-parametric bootstrap were performed.

3. Results

3.1. Sleep and emotional problems

Longitudinal comparison showed that, overall, average TIB decreased both on weekdays and weekends across adolescence. At age 14, time in bed (TIB) during the week was shorter than during the weekend by 1 h 32 min on average, with a TIB of 8 h 44 min (\pm 0 h 51 min) on weekdays and 10 h 17 min (\pm 1 h 12 min) during the weekend ($t(110) = -13.42, p < .001$). This TIB-variability decreased moderately at 19 years to approx. 1 h 16 min, with weekday TIB of 8 h 04 min (\pm 1 h 01 min) and TIB on weekends of 9 h 20 min (\pm 1 h 01 min) ($t(110) = -10.52, p < .001$; see Table 1 for sleep characteristics). Girls and boys showed comparable evolutions of change in all sleep variables (for

detailed description see Supplement S2). TIB during the week and TIB-variability correlated significantly at both time points: $r_{14\text{yrs}} = -.37, p < .001$ and $r_{19\text{yrs}} = -.62, p < .001$.

All subjects scored within the subclinical range for internalizing symptoms on the SDQ (<15) at baseline and follow-up. Over the two time points, we observed an increase in internalizing problems (Table 1). To examine the relation between sleep variables and affective symptoms, we calculated partial correlation coefficients between the longitudinal changes in sleep schedule (when participants reported to retire to bed and rise in the mornings), Δ TIB and Δ TIB-variability, with longitudinal changes in SDQ internalizing while controlling for internalizing problems at baseline, gender and age. We found a significant positive correlation between increasing Δ retire-variability and Δ internalizing symptoms, $r_p = .20, p < .05$. This indicates that the more the variability in times adolescents retire to bed between weekdays and weekends increases over the 5 years follow-up period, the steeper the increase in Δ internalizing symptoms. Changes in internalizing scores (Δ Internalizing) were negatively related to Δ TIB on weekends, $r_p = -.25, p < .01$, and to Δ TIB-variability from weekdays to weekends, $r_p = -.29, p < .01$. This indicates that from early to late adolescence, an increasing Δ TIB on weekends and Δ TIB-variability is associated with a decrease in internalizing problems. All other sleep variables were not associated with internalizing scores, all $r_p < .16$, all $p > .05$ (see Supplementary Table S3).

3.2. FA change with age

A linear mixed effects model was performed to examine the longitudinal effect of age on global FA values, controlling for gender and alcohol consumption. Age had a significant effect on FA values, $\chi^2(2) = 110.87, p < .001$, which increased from 14 years ($M = .475$) to 19 years of age ($M = .487$), $b = 0.012, t(108) = 9.98, p < .001$, as expected (Bava et al., 2010; Giorgio et al., 2010; Lebel and Beaulieu, 2011). The effect did not differ between girls and boys, $\chi^2(1) = 3.30, p = .07$, nor was there a significant interaction, $\chi^2(1) = 2.46, p = .12$.

3.3. Association between sleep characteristics and FA

The whole brain voxel-wise analysis revealed that the longitudinal change in FA was significantly correlated with Δ TIB-variability and Δ TIB on weekends. For Δ TIB-variability, there was a significant positive correlation with change in FA between 14yrs and 19yrs in 8 clusters, whereas Δ TIB on weekends was significantly correlated with 5 clusters (see Table 2, for a more detailed account including cluster subpeaks

Table 1

Participant characteristics, sleep habits (h:mm), and affective problems at Baseline (14 years), Follow-Up (19 years) and changes in these variables across the 5 year follow-up period (Δ).

		Baseline	FU	5- year differences (FU – Baseline; Δ)		Direction of change	
		Mean (SD)	Mean (SD)	Mean (SD)	t		r
Demography	Gender	53.2% (n = 59) female					
	Age	14.5 (.44)	19.8 (.62)	5.3 (.60)			
Alcohol consumption	AUDIT	1.22 (1.92)	4.29 (3.44)	3.07 (3.34)	9.68 **	.33 **	↑
Sleep Schedules	RT weekday	22:23 (0:45)	23:30 (1:03)	1:07 (1:03)	4.29 **	.38 **	↑
	RT weekend	23:30 (1:05)	1:03 (1:24)	1:33 (1:16)	12.95 **	.51 **	↑
	RT-variability	1:06 (0:48)	1:32 (1:04)	0:26 (1:08)	3.98 **	.29 *	↑
	WT weekday	07:07 (0:22)	07:34 (1:08)	0:27 (1:13)	3.9 **	-.05	↑
	WT weekend	09:47 (1:08)	10:23 (1:17)	0:36 (1:25)	4.4 **	.32 **	↑
	WT-variability	2:40 (1:12)	2:48 (1:20)	0:08 (1:41)	.88		
Sleep duration	TIB weekday	8:44 (0:51)	8:04 (1:00)	-0:40 (1:17)	-5.49 **	.04	↓
	TIB weekend	10:17 (1:12)	9:20 (1:01)	-0:57 (1:29)	-6.76 **	.11	↓
	TIB-variability	1:33 (1:13)	1:16 (1:16)	-0:17 (1:44)	-1.74		
Affective problems	SDQ total	9.19 (4.56)	9.28 (4.89)	.09 (4.6)	.21		
	SDQ internalizing	3.44 (2.65)	4.31 (3.06)	.86 (2.81)	3.25 *	.53 **	↑

Note. M, Mean; SD, Standard deviation; Δ , longitudinal difference; r = Pearson correlation coefficients as within subject effect size measure; RT, retire time; WT, wake-up time; TIB, time spent in bed; SDQ, Strength and Difficulties Questionnaire; ↓, longitudinal decrease; ↑, longitudinal increase. Times reported in hours:minutes. * $p < .05$ ** $p < .001$ (uncorrected for multiple comparisons)

Table 2

Size and localisation of peak voxels of significant clusters positively associated with longitudinal change in sleep variables from baseline to follow-up.

Cluster	Voxel number	Peak voxel coordinates			Structure	Probability ^a %
		X	Y	Z		
Δ TIB-variability						
1	4790	-30	-54	14	L Inferior fronto-occipital fasciculus	9
2	444	-28	36	19	L Anterior thalamic radiation	19
3	432	-7	23	15	Forceps Minor	20
4	141	-25	13	-1	L Inferior fronto-occipital fasciculus	39
5	84	-25	46	-1	L Inferior fronto-occipital fasciculus	15
6	32	-35	37	-2	L Uncinate fasciculus	14
7	10	-16	17	28	L Cingulum	3
8	10	-13	-37	61	L Corticospinal Tract	5
Δ TIB on weekends						
1	588	-19	-76	15	Forceps Major	21
2	85	-24	-26	11	L Corticospinal tract	23
3	44	-28	-66	3	Forceps Major	16
4	22	-32	-37	25	L Superior longitudinal fasciculus	19
5	18	-31	-57	-2	L Inferior fronto-occipital fasciculus	11

Note. Measures of Fractional Anisotropy. MNI coordinates. Structures were obtained using the JHU white-matter tractography atlas and JHU ICBM-DTI-81 white matter labels atlas. ^a Probability, that the peak voxel of the cluster is located in the given structure (only available for JHU white-matter tractography atlas). L, left; Δ, longitudinal difference (Follow-Up measurement – Baseline measurement)

refer to [Supplementary Table S4](#)).

For ΔTIB-variability, these clusters include the anterior thalamic radiation, the corticospinal tract, the cingulum (cingulate gyrus and hippocampus), body and splenium of the corpus callosum, parts of the internal capsule, forceps major and minor, superior and inferior longitudinal fasciculus, inferior fronto-occipital fasciculus as well as the

uncinate fasciculus (see [Supplementary Table S5](#)). [Fig. 1](#) shows an illustration of the association between ΔTIB-variability and FA development in L-SLF, L-IFOF and the body of the corpus callosum.

The 5 clusters associated with ΔTIB on weekends from early to late adolescence included the left anterior and posterior thalamic radiation, the left corticospinal tract and cingulum, forceps major, the left inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, the left superior longitudinal fasciculus, splenium of the corpus callosum, posterior corona radiata and parts of the left internal capsule (see [Supplementary Table S6](#)). Illustrations of this association in the L-IFOF, L-ILF, and forceps major can be found in [Fig. 2](#). There were no significant association with ΔTIB during the weekdays and FA development.

3.4. Sleep-related changes in FA and internalizing

Previous literature implicates the SLF in depressive symptoms ([Murphy and Frodl, 2011](#)) and adolescent populations at high risk for depression ([Huang et al., 2011](#)). Longitudinal changes in FA in left SLF were significantly associated with longitudinal changes in sleep behaviour, particularly TIB on weekends and TIB-variability. We performed regression analysis controlling for gender, age and alcohol consumption (ΔAUDIT) in order to explore the directionality of longitudinal changes in sleep variables and affective symptoms. An increase in both ΔTIB-variability ($\beta = -.26$, $t(107) = -3.09$, $p < .01$), and ΔTIB on weekends ($\beta = -.23$, $t(107) = -2.66$, $p < .01$) significantly predicted a decrease in Δinternalizing symptoms from early to late adolescence, while controlling for internalizing symptoms at baseline. As ΔTIB on weekends and ΔTIB-variability are significantly related, $r = .69$, $p < .001$, we calculated mediation models separately for each variable.

Causal mediation analyses were calculated using the extracted FA values from SLF in all significant voxels. Changes in FA in the SLF mediated the association between 5-year changes in TIB-on weekends (ΔTIB-on weekends) and Δinternalizing symptoms significantly, such that each point of longitudinal increase in FA in the L-SLF led to an additional decrease of internalizing symptoms of 0.9%, beyond the effect of changes in ΔTIB on weekends (see [Table 3](#) and [Fig. 3](#)). ΔTIB-variability mediated this association with marginal significance (see

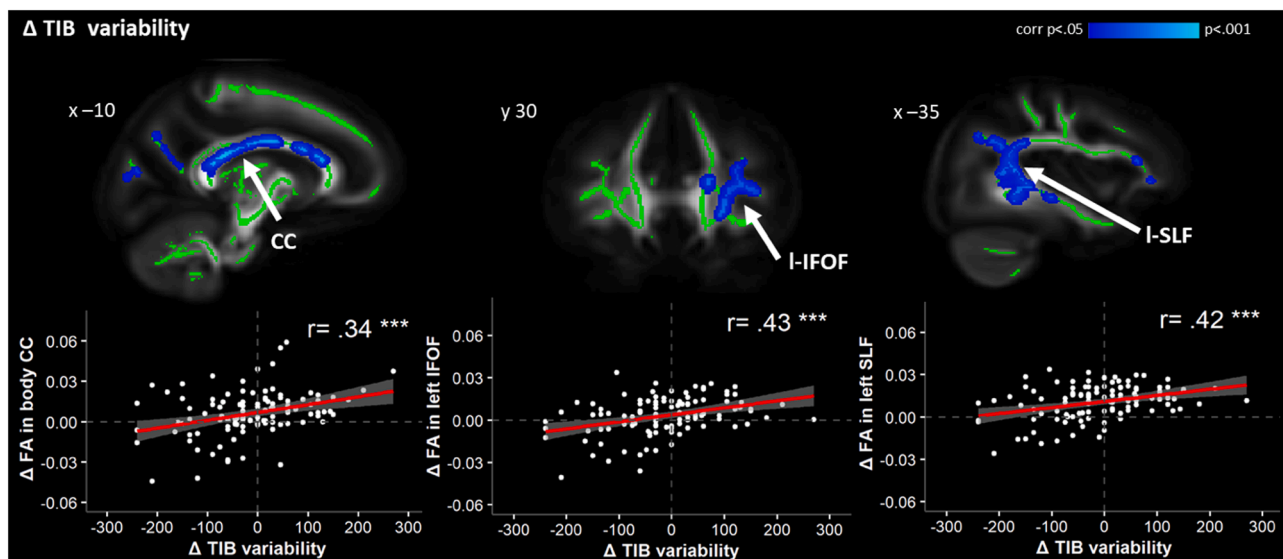


Fig. 1. Illustration of regions showing significant correlations (in blue) between ΔTIB-variability between weekends and weekdays (in minutes) and ΔFA. The longitudinal ΔTIB-variability shown in this figure is calculated by subtracting TIB-variability at baseline from TIB-variability at follow-up. Thus, a positive value of ΔTIB-variability indicates greater TIB-variability (more catch-up sleep) at Follow-up compared to Baseline, i.e. an increase in TIB-variability. Scatterplots showing visual depiction of this relationship in left superior longitudinal fasciculus (L-SLF; sagittal view), body of the corpus callosum (CC; sagittal view) and left inferior fronto-occipital fasciculus (L-IFOF; coronal view). Note. * $p < .05$; ** $p < .01$; *** $p < .001$. Significant results are displayed at $p < 0.05$ FWE corrected on study specific FA skeleton and mean FA mask (in green) using `tbss_fill`. Images are presented in radiological convention. MNI coordinates.

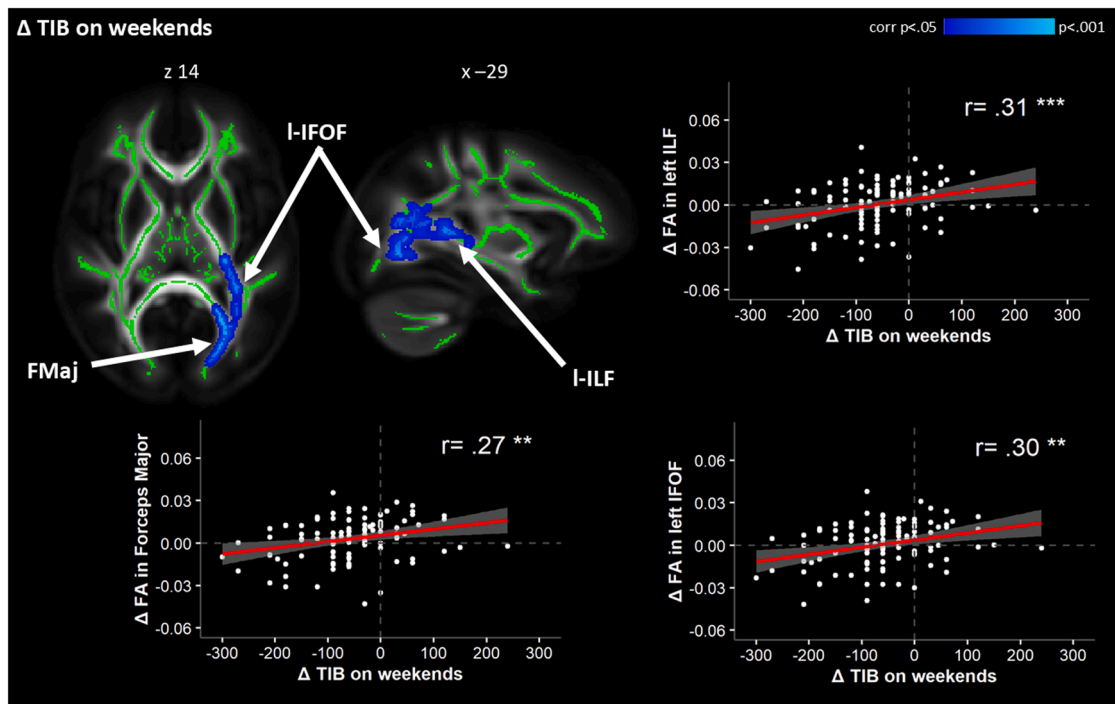


Fig. 2. Regions of FA and illustration of significant correlations (in blue) between Δ TIB on weekends (in minutes) and Δ FA. The longitudinal Δ TIB on weekends shown in this figure is calculated by subtracting TIB on weekends at baseline from TIB on weekends at follow-up. Negative values indicate less time in bed on weekends from baseline to follow-up, whereas positive numbers indicate increased time in bed on weekends from baseline to follow-up. Scatterplots showing visual depiction of this relation in forceps major (FMaj), left inferior fronto-occipital fasciculus (l-IFOF) and left inferior longitudinal fasciculus (l-ILF). Note. * $p < .05$; ** $p < .01$; *** $p < .001$. Significant results are displayed at $p < 0.05$ FWE corrected on study specific FA skeleton and mean FA mask (in green) using `tbss_fill`. Images are presented in radiological convention. MNI coordinates.

Table 3. We also explored mediation effects in other fascicles previously associated with depressive symptoms, such as corpus callosum, IFOF and uncinate and report them in [Table 3](#).

4. Discussion

We explored the longitudinal association between sleep behaviour with adolescent white-matter maturation and whether this is related to internalizing problems in otherwise healthy adolescents. We found that the longitudinal change of fractional anisotropy (FA) in a number of tracts was *positively* associated with changes in both the time adolescents spent in bed on weekends, and the variability of this time period from weekday to weekends (i). Furthermore, we found that Δ TIB-weekends was significantly associated with the evolution of internalizing problems over adolescence and that this association was mediated by changes in FA in the superior longitudinal fasciculus as a function of Δ TIB-weekends (ii). We observed an increase of global FA from 14–19 years of age, corroborating studies showing continued white matter maturation until late adolescence (Bava et al., 2010; Giorgio et al., 2010). The behavioural sleep changes we observed in this work support previous reports of decreasing TIB and the temporal evolution of sleep schedules in the adolescent life-phase (National Sleep Foundation, 2006).

Here, we found that sleep behaviour is associated with have long-term changes in white matter development during adolescence. The 5-year change in time an adolescent spends in bed covaried significantly with white matter development in a number of important left-lateralized projection and association fibres involved in both emotional and cognitive processes, including the left superior and inferior longitudinal fasciculi (SLF and ILF), left inferior fronto-occipital fasciculus (IFOF) and the corpus callosum. The SLF is a long association fibre connecting the prefrontal to parietal cortex and plays an important role in higher-level cognitive processes (Sasson et al., 2013; Wise, 2003). The ILF and IFOF are associative tracts, which connect occipital and temporal

lobes, as well as occipital and orbitofrontal cortex. The corpus callosum, an interhemispheric fibre bundle connecting frontal with parietal areas, and the uncinate fasciculus (UF), spreading from the lateral orbitofrontal cortex to the anterior portion of the temporal lobe (Catani and Thiebaut de Schotten, 2008), are directly involved in affective and reward processing, as well as emotion regulation (Von Der Heide et al., 2013).

Our results imply that spending more time in bed on weekends compared to weeknights (an increase in TIB-variability and TIB on weekends), as well as spending more time in bed on weekends from early to late adolescence, might have favourable effects on white matter development in these tracts, given that FA values primarily reflect the integrity of developing white matter tracts (Soares et al., 2013; Westlund Schreiner et al., 2020). However, changes in FA might be influenced by multiple tissue characteristics, including axonal diameter, fibre density, regional myelination or fibre crossings (Winklewski et al., 2018). An additional analysis of radial (RD) and mean diffusivity (MD) would be helpful to delineate the exact microstructural changes associated with FA and therefore allow further interpretation of underlying microstructure and associated function. Although most studies report evidence of decreased white matter integrity (reflected in decreased FA and/or increased MD/RD) in adolescent depression (e.g. Geng et al., 2016; Lewinn et al., 2014; Zhou et al., 2022), or at risk-populations (Huang et al., 2011), some work also shows conflicting results as to increased or decreased FA in adolescent depression (Aghajani et al., 2014; Cullen et al., 2020), or no effects (van Velzen et al., 2020), and mixed findings concerning internalizing symptoms in adolescents (Andre et al., 2020; Jarvers et al., 2022; Roelofs et al., 2022). Given that our data showed a negative association of TIB-related FA changes and internalizing problems, these data point to the interpretation, that long term increases in weekend catch-up sleep associate favourably with white matter change, possibly driven by increased white matter integrity through myelination in adolescence.

Table 3

Results of the mediation analysis between longitudinal sleep changes and Δ internalizing symptoms from 14–19 years with Δ FA in significant tracts as mediator and age at baseline, gender and time interval and alcohol consumption (Δ AUDIT) as confounding variables.

	Mediation effect (95% CI)	Direct Effect (95% CI)	Total Effect (95% CI)	Proportion mediated (%)
Δ TIB variability				
L SLF temporal part	-.06 (-.18 to .03)	-.19 [†] (-.39 to .03)	-.26 * (-.44 to -.06)	25
L SLF	-.08 [†] (-.20 to .01)	-.17 (-.37 to .03)	-.26 ** (-.45 to -.05)	32 [†]
Splenium of Corpus Callosum	-.04 (-.12 to .01)	-.21 * (-.39 to -.01)	-.26 * (-.43 to -.06)	17
Body of Corpus Callosum	-.03 (-.11 to .04)	-.23 * (-.42 to -.04)	-.26 * (-.44 to -.06)	11
L IFOF	-.05 (-.15 to .03)	-.21 [†] (-.40 to .02)	-.26 * (-.44 to -.05)	19
L Uncinate	-.02 (-.10 to .06)	-.24 * (-.43 to -.02)	-.26 * (-.44 to -.06)	6
Δ TIB on weekends				
L SLF temporal part	-.07 * (-.18 to 0)	-.15 (-.35 to .05)	-.22 * (-.43 to -.03)	33 [†]
L SLF	-.09 * (-.19 to -.01)	-.13 (-.35 to .07)	-.22 * (-.43 to -.03)	41 *
Splenium of Corpus Callosum	-.02 (-.07 to .01)	-.20 * (-.41 to -.01)	-.22 * (-.43 to -.03)	10
L IFOF	-.05 (-.05 to .05)	-.17 (-.38 to .03)	-.22 (-.38 to -.04)	25

Note. Point estimates and confidence intervals with upper and lower boundaries in parentheses. * $p < .05$; ** $p < .01$; [†] $p < .1$; Δ , longitudinal difference (Follow-Up measurement – Baseline measurement); FA, fractional anisotropy; SLF, superior longitudinal fasciculus; ILF, left inferior longitudinal fasciculus; IFOF, inferior fronto-occipital fasciculus, L, left.

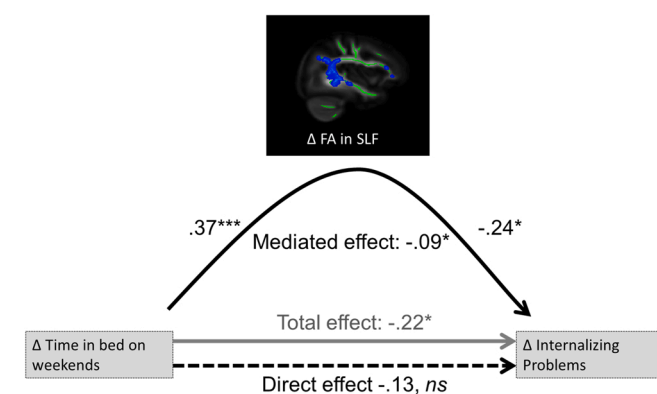


Fig. 3. Results of mediation analysis. The association between Δ TIB-weekends and Δ internalizing problems was mediated by the effects of 5-year changes in sleep behaviour on white matter development in left Superior Longitudinal Fasciculus (L-SLF). * $p < .05$; ** $p < .01$, *** $p < .001$; ns, not significant; Δ , longitudinal difference (Follow-Up measurement – Baseline measurement).

This pattern of sleep behaviour can be interpreted as a catch-up strategy to compensate for increasing accumulation of sleep debt during the week and is common phenomenon in adolescence (Owens and Adolescent Sleep Working Group, 2014; Roberts et al., 2009; National

Sleep Foundation, 2006). The present findings are the first to suggest a positive association between compensatory sleep and brain development. Most previous studies suggest adverse effects of chronic sleep loss which cannot be reversed with compensatory sleep (Cohen et al., 2010). In line with this, children with higher weekend to weekday sleep duration variability demonstrate more suicidal ideation (Kang et al., 2014) and those who show stable and sufficient sleep behaviour are more physically active and less obese than children with shorter sleep times (Stone et al., 2013). However, if children accumulate a sleep debt during the week (i.e. when sleep duration during the week is insufficient), those that catch-up on sleep on the weekend are less obese, than those who do not catch up on lost sleep (Kim et al., 2012; Stone et al., 2013). In fact, catching-up on sleep on weekends, as it is often reported in adolescents, also has positive influences on a number of sleep related health issues such as hypertension, the metabolism and the Body-Mass Index (Hwangbo et al., 2013; Im et al., 2017; Killick et al., 2015; Kim et al., 2012), as well as on neurocognitive functions (Kuula et al., 2015). Moreover, a recent study reports that a moderate amount of catch-up sleep decreases the odds of depressive symptoms and suicidal ideation in adolescents, but has to be related to the amount of sleep acquired during the week (Lee et al., 2022) that is, catch-up sleep is useful when it is needed. It can therefore be speculated that the ability to catch up sleep on weekends represents the ability of the individual to recover from sleep loss, and emerge as a resilience factor during adolescent development. According to our behavioural data, this compensatory mechanism might decrease over time, with sleep duration shortening during weekdays and weekends and moderate decreases in TIB-variability as adolescents start to approach an age where maturation is largely complete.

Sleep patterns during adolescence may affect brain grey and white matter differently. We have previously shown in a cross-sectional study that short sleep duration during the week and late sleep times on weekends correlate with smaller regional grey matter volumes (Urrila et al., 2017). In a previous study by Telzer et al., irregularity of sleep patterns on a day-to-day basis predicted decreases in white matter FA 1.5 years later, but, in contrast to the present findings, weekday to weekend sleep duration variability was not found to have any effect (Telzer et al., 2015). We speculate that a variable sleep schedule across the whole week would reflect a more chaotic lifestyle and be more detrimental to the developing white matter than weekday-to-weekend variability. The discrepancies between the findings by Telzer et al. and our findings may also be accounted for by a considerably longer follow-up time (5 years vs. 1.5 years), and a longitudinal DTI approach in our study. It is possible that sleep affects white matter differently at different phases of adolescent development, sleep variability being more detrimental e.g. in the earlier phases of development, and the ability to catch-up sleep becoming more and more important as adolescents mature.

Taken together, current evidence suggest that while insufficient weekday sleep, and late-prone weekend sleep schedules might have a short-term detrimental effect on grey matter (Taki et al., 2012; Urrila et al., 2017), sleep might impact white matter development on the long-term (Jamieson et al., 2021; Telzer et al., 2015). The present findings advance this literature in suggesting, that a compensatory weekend sleep might serve a long-term protective function for white matter development. Based on the wealth of evidence on the negative impact of sleep debt on physical and mental health and cognition (Baum et al., 2014; Carli et al., 2014; Roberts et al., 2009; Short and Louca, 2015; Talbot et al., 2010), we would not advise adolescents to cut down their sleep during the week. Instead, based on our findings, it might be advisable to allow adolescents to sleep sufficiently on weekends, in particular if they have accumulated a sleep debt during the week. Effort should thus be dedicated to improve adolescents' possibilities to obtain enough sleep both during the week as well as during the weekend to promote optimal brain development.

While internalizing symptoms increased from early to late

adolescence, we found increases in irregularity of retiring to bed between weekdays and weekends might accelerate this association. This is in line with previous studies, suggesting adverse effects of irregular sleep patterns on affective well-being (Biggs et al., 2011; Fuligni and Hardway, 2006). Interestingly, we found that compensatory weekend sleep might counteract this association, such that longer sleep on weekends from early to late adolescence (Δ TIB-weekends) and coinciding increases in FA in the left superior longitudinal fasciculus, were associated with a decrease in internalizing problems across time. This could be consistent with the role of catch-up sleep in conserving a typical maturation in white matter microstructure, reflected in FA increases throughout adolescence (Bava et al., 2010; Giorgio et al., 2010; Lebel and Beaulieu, 2011).

Our findings add to the literature showing an interaction between sleep and changed structural connectivity in fronto-parietal and cortico-subcortical regions previously associated with depressive symptoms in adolescents (Aghajani et al., 2014; Geng et al., 2016; Huang et al., 2011; Lewinn et al., 2014; Zhou et al., 2022) and add to studies showing associations between internalizing / externalizing behaviours and white matter microstructure over time (Andre et al., 2020; Jarvers et al., 2022; Roelofs et al., 2022). Surprisingly, longitudinal changes in FA were predominantly found in left-lateralized tracts. A previous longitudinal study reports FA changes across childhood development more strongly in the left hemisphere (Eluvathingal, Hasan, Kramer, Fletcher, and Ewing-Cobbs, 2007; Krogsrud et al., 2016, but see Uda et al., 2015 for contrasting results). Interestingly however, reduced FA in the left SLF, the corpus callosum and ILF have been repeatedly reported in relation to depression (Liao et al., 2013; Murphy and Frodl, 2011) and mood disorders (Jenkins et al., 2016) and reduced FA in these tracts has been suggested to be a familial risk factor in the development of depression in this age group (Huang et al., 2011). Two recent meta-analyses of FA differences in depression have shown consistent reductions in FA particularly in the left SLF (Jenkins et al., 2016; Murphy and Frodl, 2011). Moreover, increased FA, in SLF, IFOF, uncinate fasciculus and corpus callosum, in overlapping with the tracts identified in this study, has been found in healthy individuals with familial risk of developing depression and adverse childhood experiences compared to those without such experiences (Frodl et al., 2010). This gene-environment interaction suggests an increased structural connectivity in these fibres might be a neurobiological factor of resilience to depression. In line with these reports, catch-up sleep on weekends might positively impact white matter maturation in relevant fibres and, thus, decrease the occurrence of internalizing problems.

In contrast to most previous reports on cross-sectional interactions between sleep and brain development in pediatric samples, our analysis involved a longitudinal design with phenotypic and DTI measures repeated 5 years apart in adolescents recruited at the same age in the community. Nevertheless, the correlational design used cannot infer causality. Sleep behaviour, white matter development and internalizing symptoms most probably affect one another in a bidirectional manner (Gregory and Sadeh, 2012; Paus et al., 2008; Telzer et al., 2015). Furthermore, additional factors not reported in this work impact and co-vary with sleep behaviour and internalizing problems e.g. social networks, peer group, academic performance, personality traits or genetic predispositions.

To measure sleep schedules, we acquired subjective sleep reports. Importantly, as the TIB variable is the difference between retire and wake-up times, we therefore cannot make claims about the sleep duration, but rather how much time adolescents spent in bed. Objective sleep measures, such as polysomnography or actigraphy repeated over several nights, could have given a more reliable estimate of the adolescents' sleep. Given the sample size, long follow-up period, and otherwise extensive research protocol, however, adding them to our study was not feasible, and could potentially have increased drop-out rate during follow-up. Subjective sleep measures are much less burdensome for the participants and more suitable for studying larger samples

representative of the population. While longitudinal changes in adolescents' reporting accuracy are possible, a recent 2-year longitudinal study comparing adolescents' subjective and actigraphic bedtime measures reported that these measures were correlated at both time points (Brychta et al., 2019), confirming previous observations that self-report and actigraphy measure the same underlying parameter in adolescents (Wolfson et al., 2003). Further, Brychta et al. reported that on school nights, the self-report and actigraphy measures did not differ in group-level sensitivity to changes in bedtime. Also, non-school nights self-reported bedtimes changed less than actigraphy-measured bedtimes. Thus, assuming a transposition of these authors' findings to the present study, we may speculate that the weekend self-reported bedtime variability might be underestimated in the present study, raising only the risk of false negative findings.

Lastly, The SDQ questionnaire assesses internalizing problems over a period of 6 months. We computed post-hoc regression analysis, which showed that internalizing scores at baseline predicted scores at follow-up ($b=.61$, $t(109) = 6.44$, $p < .001$, adjusted $R^2 = .27$). Although this lends support to the notion, that internalizing problems are associated over time, we can make no final inferences on the trajectory of internalizing problems over entirety of the 5 year period.

In conclusion, the association between change in sleep behaviour and white-matter maturation and emotional problems was detected using a longitudinal design in adolescents. Catch-up sleep might represent a natural compensatory mechanism for developmental brain maturation, and serve as a protective factor for the long-term development of internalizing symptoms. The need to examine this link further is evident in order to develop targeted preventive strategies and identification of high-risk populations for affect disorders.

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CRediT authorship contribution statement

Conceptualization: JLM, ASS, EA and MLP; Methodology: JLM, ASS, EA, SG, JM, GJB, HL and HV; Formal Analysis: SG, HL and HV; Data curation: HL, SG, ASS, JP, PBF, DPO; Investigation: JLM, EA, IF, PBF RM and SG; Writing – Original Draft Preparation: SG and ASS; Writing – Review & Editing: JLM, HL, MLP; Visualization: SG, HL; Supervision: JLM; Project Administration JLM, GS, VF, TP, ALB, UB, CB, PC, SD, HF, JG, HG, PG, FN, MS; Funding Acquisition: JLM, MLP, GS, TB, HG, SD, HF, AH, MS.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr Banaschewski served in an advisory or consultancy role for ADHS digital, Infectopharm, Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Roche, and Takeda. He received conference support or speaker's fee by Medice and Takeda. He has been involved in clinical trials conducted by Shire & Viforpharma. He received royalties from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press. He has been involved in clinical trials conducted by Shire & Viforpharma. Dr Barker has received honoraria from General Electric Healthcare for teaching on scanner programming courses. Dr Barker has received honoraria from General Electric Healthcare for teaching on scanner programming courses. Dr Gowland has received a research grant from Lyndra and an honorarium paid to her employer from GlaxoSmithKline. The present work is unrelated to the above grants and relationships.

Data Availability

Data will be made available on request.

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Competing Interests

Dr Banaschewski served in an advisory or consultancy role for ADHS digital, Infectopharm, Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Roche, and Takeda. He received conference support or speaker's fee by Medice and Takeda. He has been involved in clinical trials conducted by Shire & Viforpharma. He received royalties from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press. He has been involved in clinical trials conducted by Shire & Viforpharma. Dr Barker has received honoraria from General Electric Healthcare for teaching on scanner programming courses. Dr Barker has received honoraria from General Electric Healthcare for teaching on scanner programming courses. Dr Gowland has received a research grant from

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.dcn.2022.101193](https://doi.org/10.1016/j.dcn.2022.101193).

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