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Article

Evidence of Genetic Overlap Between Circadian Preference and Brain White Matter Microstructure

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Abstract

Several neuroimaging studies have reported associations between brain white matter microstructure and chronotype. However, it is unclear whether those phenotypic relationships are causal or underlined by genetic factors. In the present study, we use genetic data to examine the genetic overlap and infer causal relationships between chronotype and diffusion tensor imaging (DTI) measures. We identify 29 significant pairwise genetic correlations, of which 13 also show evidence for a causal association. Genetic correlations were identified between chronotype and brain-wide mean, axial and radial diffusivities. When exploring individual tracts, 10 genetic correlations were observed with mean diffusivity, 10 with axial diffusivity, 4 with radial diffusivity and 2 with mode of anisotropy. We found evidence for a possible causal association of eveningness with white matter microstructure measures in individual tracts including the posterior limb and the retrolenticular part of the internal capsule; the genu and splenium of the corpus callosum and the posterior, superior and anterior regions of the corona radiata. Our findings contribute to the understanding of how genes influence circadian preference and brain white matter and provide a new avenue for investigating the role of chronotype in health and disease.

Keywords: Chronotype; circadian preference; white matter microstructure; diffusion tensor imaging; genetics; complex traits; epidemiology

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Circadian rhythms are physiological processes accompanied by behavioral changes that follow a ˜24-hour period in most living organisms. Humans are normally diurnal creatures, and biological clocks endogenously control their activity–rest patterns. Notably, these cycles have profound effects on fundamental molecular and behavioral processes (Jones et al., 2019).

The expression of circadian preference, often referred to as chronotype, is the natural phenomena accounting for the variation in an individual's preference for early or late sleep and activity driven by sleep–wake cycles due to internal circadian rhythms (Jones et al., 2019). Furthermore, chronotype defines whether an individual is a *morning person*, implying a preference for going to bed and waking up early, or an *evening person*, meaning someone who prefers later sleep and waking up times. A considerable proportion of chronotype variance is due to factors such as age, gender and the exposure to different levels of light. However, genetic variation also accounts for chronotype differences, and twin studies have estimated its heritability at ∼50% (Allebrandt et al., 2014; Duffy & Czeisler, 2002; Kalmbach et al., 2017; Leocadio-Miguel et al., 2017).

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Adequate sleep is vital for healthy brain function and physiological systems (Medic et al., 2017). The *restoration theory* states that sleep is essential to replete and restore the cellular components necessary for biological functions (Brinkman & Sharma, 2020). In contrast, the *brain plasticity theory* describes the vital neural reorganization and development of the brain's diverse structures and functions during the restorative state (Brinkman & Sharma, 2020). Recently, circadian parameters such as chronotype, average mid-sleep and social jetlag have been described as predictors of sleep quality (Harfmann et al., 2020).

Brain white matter constitutes half of the brain, being a fundamental element of neural networks responsible for neurobehavioral activity, including sleep duration and REM sleep (Altendahl et al., 2020; Filley & Fields, 2016; Yaffe et al., 2016). Diffusion-weighted imaging is a noninvasive neuroimaging technique that can be used to characterize the brain's white matter integrity in acute sleep deprivation, insomnia and chronotype (Lu et al., 2017; Wei et al., 2019). In particular, diffusion tensor imaging (DTI) refers to the implementation of a tensor model to explore the main directions (eigenvectors of the model) and magnitude (eigenvalues) of water diffusivity (Basser et al., 1994), which are sensitive to the underlying microstructure (Beaulieu, 2002). Water diffusivity parameters, measured through DTI, include axial diffusivity (AD), radial diffusivity (RD), mean diffusivity (MD), fractional anisotropy (FA) and mode of anisotropy (MO).

DTI, being a useful tool to explore brain regions with single fiber orientation, is used to infer histological changes in normal development and pathology. For instance, AD is associated with axonal integrity, while RD is related to axonal density, myelin integrity, axonal diameter and fiber coherence (Beaulieu, 2002).

Genome-wide association studies (GWAS) of neuroimaging measures have uncovered 213 independent significant genetic variants associated with 90 DTI parameters (Zhao et al., 2019) and 351 loci with chronotype (Jones et al., 2019). Also, neuroimaging studies have identified white matter differences in *evening people* (Rosenberg et al., 2014). Studies investigating the disruption of circadian cycles show that a day of wakefulness is associated with increases in white matter FA due to RD reductions (Elvsåshagen et al., 2015; Voldsbekk et al., 2020), thus suggesting that wakefulness-related effects may regulate white matter (Voldsbekk et al., 2020).

It is unclear whether the association between white matter and sleep is due to genetic factors, and if so, whether pleiotropic or causal effects drive the association. In the present study, we address this question by leveraging GWAS summary statistics data sets to estimate whole-genome genetic correlations using LD score regression. Also, we assess causality between DTI measures for white matter and circadian preference using Mendelian randomization analysis. Our results provide new insights into the relationship between chronotype and white matter structure and contribute to our understanding of the genetic and neurological factors underlying chronotype.

Materials and Methods

Discovery GWAS for Circadian Preference

This study used summary statistics from GWAS for self-reported chronotype ($N = 449{,}734$). Summary statistics include allele frequency, effect size, standard error, as well as the p value of every genetic variant that was tested on the trait of interest. These GWAS summary statistics were obtained from samples with European ancestry from the repository of its corresponding publication (Jones et al., 2019). Chronotype was assessed as a single self-reported measure (Field-ID: 1180): 'Do you consider yourself to be?' with six possible answers including 'Definitely a *morning* person', 'More a *morning* than *evening* person', 'More an *evening* than a *morning* person', 'Definitely an *evening* person', 'Do not know' or 'Prefer not to answer' (Jones et al., 2019). Here, chronotype was assessed as a dichotomous variable with two levels, including being a *morning* or an *evening* person. Chronotype GWAS summary statistics were adjusted for age, sex, study center and genotyping array (Jones et al., 2019). A full description of GWAS summary statistics used in this study is available in its corresponding publication (Jones et al., 2019).

Discovery GWAS for DTI Brain Measures

The present study used summary statistics from GWAS with European ancestry for white matter microstructure, particularly DTI, objectively measured with magnetic resonance imaging (MRI) and has units of $mm^2\ s^{-1}$. The GWAS summary statistics used here were obtained from samples with European ancestry ($N = 17{,}706$) from a public repository as reported in its corresponding publication (Zhao et al., 2019). For instance, UK Biobank imaging data were processed according to the automated processing and quality control pipeline described in previous studies (Alfaro-Almagro et al., 2018; Zhao et al., 2019), and white matter tracts were labeled following the ENIGMA-DTI pipeline (Jahanshad et al., 2013; Kochunov et al., 2014; Zhao et al., 2019). White matter microstructure parameters included mean diffusivities (MD), axial diffusivities (AD), radial diffusivities (RD) mode of anisotropies (MO) and FA. These five parameters were measured in 21 brain regions and all regions combined (Zhao et al., 2019). GWAS were adjusted for age, age-squared, sex, age*sex interaction, age-squared*sex interaction, and the top 10 genetic principal components (Zhao et al., 2019). A full description of the DTI preprocessing and the DTI analysis and imaging quality control procedures is available in the supplementary information of its corresponding publication (Zhao et al., 2019).

Genetic Correlations Analyses

We performed LD score regression (Bulik-Sullivan, Loh et al., 2015) using GWAS summary statistics as implemented in the Complex Trait Genomics Virtual Lab (CTG-VL, http://genoma.io; Cuéllar-Partida et al., 2019) to estimate genetic correlations between chronotype and white matter microstructures. Briefly, CTG-VL uses the analysis software PLINK to clump and estimate linkage-disequilibrium between SNPs (Cuéllar-Partida et al., 2019). Only samples with European ancestry were used to avoid potential biases regarding population differences in linkage-disequilibrium and allele frequencies. Benjamini-Hochberg's false discovery rate (FDR < 5%) was used to account for multiple testing.

Mendelian Randomization

Mendelian randomization (MR) is a method used in epidemiology to assess causal relationships between phenotypes, environmental exposures or disease outcomes (Davies et al., 2018; Swerdlow et al., 2016; Zhu et al., 2018). We used two-sample generalized summary-data-based Mendelian randomization (GSMR; Zhu et al., 2018), a method that uses genetic instruments strongly associated (i.e., genome-wide significant SNPs) with the outcome, to perform bidirectional analyses and assess possible causal relationships between chronotype and 29 DTI parameters that displayed a significant genetic correlation. *P* values were corrected for multiple testing using Benjamini–Hochberg's FDR (FDR < 5%). Both corrected and uncorrected *p* values are reported.

Results

Genetic Correlations

From the 110 DTI parameters that were analyzed, we identified 29 significant negative genetic correlations (FDR < 5%) between chronotype and DTI parameters (Table 1). Negative correlations with chronotype imply an increase in eveningness, that is, a preference for late sleep patterns and activity. The average MD, AD and RD for all tracts showed significant negative genetic correlations with chronotype. When exploring the individual tracts (Figure 1), 10 out of 26 genetic correlations involved MD, 10 included AD, four implicated RD and two involved MO. No significant genetic correlations were identified with FA.

For MD, the strongest genetic correlations with chronotype were observed for the internal capsule, particularly in its posterior limb ($r_G = -.21$, p value $= 4.76 \times 10^{-04}$) and the retrolenticular region ($r_G = -.20$, p value $= 3.00 \times 10^{-03}$). Further, the most significant genetic correlation was identified in the splenium of the corpus callosum ($r_G = -.19$, p value $= 4.31 \times 10^{-06}$), but the genu ($r_G = -.13$, p value $= 8.92 \times 10^{-04}$) and body ($r_G = -.14$, p value $= 1.05 \times 10^{-03}$) of the corpus callosum were also genetically correlated with being an evening person. In addition, the posterior

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Table 1. White matter microstructure measures genetically correlated with chronotype

Tract	DTI parameter	*r*G	*r*G *SE*	*r*G pval
Average across all tracts	Mean diffusivity	−.14	.04	3.80 E-04
Average across all tracts	Axial diffusivity	−.14	.04	7.16 E-04
Average across all tracts	Radial diffusivity	−.13	.04	2.03 E-03
Posterior limb of internal capsule	Mean diffusivity	−.21	.06	4.76 E-04
Retrolenticular part of internal capsule	Mean diffusivity	−.20	.07	3.00 E-03
Splenium of corpus callosum	Mean diffusivity	−.19	.04	4.31 E-06
Sagittal stratum (include inferior longitudinal fasciculus and inferior fronto-occipital fasciculus)	Mean diffusivity	−.18	.06	3.89 E-03
Superior fronto-occipital fasciculus (could be a part of anterior internal capsule)	Mean diffusivity	−.16	.06	8.86 E-03
Body of corpus callosum	Mean diffusivity	−.14	.04	1.05 E-03
Genu of corpus callosum	Mean diffusivity	−.13	.04	8.92 E-04
Posterior corona radiate	Mean diffusivity	−.13	.05	4.11 E-03
Superior corona radiate	Mean diffusivity	−.12	.04	7.20 E-03
Anterior corona radiate	Mean diffusivity	−.10	.04	1.31 E-02
Retrolenticular part of internal capsule	Axial diffusivity	−.22	.06	6.42 E-04
Superior corona radiate	Axial diffusivity	−.21	.05	6.57 E-05
Posterior limb of internal capsule	Axial diffusivity	−.19	.05	3.82 E-04
Sagittal stratum (include inferior longitudinal fasciculus and inferior fronto-occipital fasciculus)	Axial diffusivity	−.18	.07	1.09 E-02
Splenium of corpus callosum	Axial diffusivity	−.16	.05	9.43 E-04
Corticospinal tract	Axial diffusivity	−.15	.06	1.28 E-02
Anterior corona radiate	Axial diffusivity	−.13	.05	6.32 E-03
Genu of corpus callosum	Axial diffusivity	−.13	.05	7.36 E-03
Superior fronto-occipital fasciculus (could be a part of anterior internal capsule)	Axial diffusivity	−.13	.05	7.71 E-03
Superior longitudinal fasciculus	Axial diffusivity	−.09	.04	1.29 E-02
Sagittal stratum (include inferior longitudinal fasciculus and inferior fronto-occipital fasciculus)	Radial diffusivity	−.15	.05	6.61 E-03
Body of corpus callosum	Radial diffusivity	−.13	.05	8.62 E-03
Splenium of corpus callosum	Radial diffusivity	−.13	.05	6.56 E-03
Posterior corona radiate	Radial diffusivity	−.12	.04	8.62 E-03
Superior corona radiate	Mode of anisotropy	−.18	.06	9.48 E-04
Retrolenticular part of internal capsule	Mode of anisotropy	−.15	.06	7.11 E-03

Note: This table shows all the diffusion tensor imaging (DTI) measures with a significant false discovery rate (FDR < 5%) genetic correlation (r_G) with chronotype. A negative genetic correlation ($r_G < 0$) indicates an association with eveningness, whereas a positive genetic correlation ($r_G > 0$) reflects an association with morningness. No significant positive correlations were identified. Results for all genetic correlations are reported in Supplementary File 1.

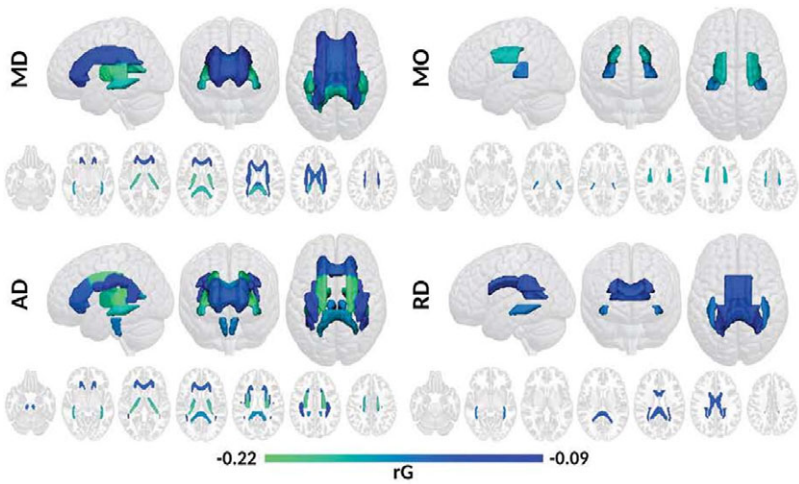

Fig. 1. Significant genetic correlations between chronotype and DTI parameters classified by individual tracts including mean diffusivity (MD), mode of anisotropy (MO), axial diffusivity (AD) and radial diffusivity (RD). All genetic correlations are negative. Negative correlations with chronotype imply a tendency to be an evening person.

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Table 2. Mendelian randomization results for chronotype and DTI

Tract	DTI parameter	Effect estimate	*SE*	*p* value	Corrected *p* value
Superior fronto-occipital fasciculus (could be a part of anterior internal capsule)	Mean diffusivity	−.11	.039	.005	.063
Splenium of corpus callosum	Mean diffusivity	−.11	.040	.006	.063
Superior corona radiata	Mean diffusivity	−.10	.039	.014	.077
Anterior corona radiata	Mean diffusivity	−.09	.039	.016	.077
Retrolenticular part of internal capsule	Mean diffusivity	−.10	.041	.020	.077
Posterior limb of internal capsule	Mean diffusivity	−.09	.041	.036	.093
Posterior corona radiata	Mean diffusivity	−.08	.040	.042	.093
Anterior corona radiata	Axial diffusivity	−.11	.041	.006	.063
Genu of corpus callosum	Axial diffusivity	−.10	.039	.014	.077
Superior corona radiata	Axial diffusivity	−.09	.039	.025	.077
Superior longitudinal fasciculus	Axial diffusivity	−.09	.040	.027	.077
Splenium of corpus callosum	Radial diffusivity	−.09	.041	.022	.077
Posterior corona radiata	Radial diffusivity	−.08	.041	.041	.093

Note: DTI, diffusion tensor imaging. One-way causal relationships between chronotype (exposure) and white matter microstructure parameters (outcome) are shown here. Negative effect estimates with chronotype imply a tendency to be an evening person. This means that eveningness is causally associated with increases in radial, axial and mean diffusivities. Corrected *p* values (false discovery rate < 5%) are referred to as *pval corrected*. Results for all 29 Mendelian randomization tests are reported in Supplementary File 2.

($r_G = -.13$, p value $= 4.11 \times 10^{-03}$), superior ($r_G = -.12$, p value $= 7.20 \times 10^{-03}$) and anterior ($r_G = -.10$, p value $= 1.31 \times 10^{-02}$) regions of the corona radiata were also genetically correlated with chronotype. A similar pattern was observed for the sagittal stratum and the superior fronto-occipital fasciculus.

Regarding AD, robust genetic correlations were identified in the corona radiata, with the most significant one in the superior region ($r_G = -.21$, p value $= 6.57 \times 10^{-05}$). The anterior region of the corona radiata was also genetically correlated with chronotype ($r_G = -.13$, p value $= 6.32 \times 10^{-03}$). Moreover, genetic correlates were observed for the retrolenticular regions ($r_G = -.22$, p value $= 6.42 \times 10^{-04}$) and the posterior limb of the internal capsule ($r_G = -.19$, p value $= 3.82 \times 10^{-04}$), followed by the splenium ($r_G = -.16$, p value $= 9.43 \times 10^{-04}$) and genu ($r_G = -.13$, p value $= 7.36 \times 10^{-03}$) of the corpus callosum. More genetic correlations were uncovered for the superior fronto-occipital fasciculus, the superior longitudinal fasciculus, the sagittal stratum and the corticospinal tract.

Genetic correlations identified between chronotype and RD included the splenium ($r_G = -.13$, p value $= 6.56 \times 10^{-03}$) and body ($r_G = -.13$, p value $= 8.62 \times 10^{-03}$) of the corpus callosum, the posterior region of the corona radiata ($r_G = -.12$, p value $= 8.62 \times 10^{-03}$) and the sagittal stratum ($r_G = -.15$, p value $= 6.61 \times 10^{-03}$). In contrast, MO displayed moderate genetic correlates with chronotype in the superior region of the corona radiata ($r_G = -.18$, p value $= 9.48 \times 10^{-04}$) and the retrolenticular section of the internal capsule ($r_G = -.15$, p value $= 7.11 \times 10^{-03}$).

Mendelian Randomization

To further explore the associations between chronotype and DTI, we performed a two-sample GSMR (Zhu et al., 2018) and assessed the potential of the 29 genetic correlations we identified to be explained by a causal association (Supplementary File 2).

We observed 13 one-way causal relationships in which an evening chronotype influences increases in mean, axial and radial diffusivities (Table 2). GSMR results suggest that eveningness exerts a causal effect on higher MD for the superior fronto-occipital fasciculus (p value $= .005$) and the reticular region and posterior limb (p value $= .006$) of the internal capsule. Further, increases in mean and axial diffusivities for the posterior corona radiata and the splenium of the corpus callosum were found to be causally influenced by an evening chronotype. A similar pattern was observed for mean and radial diffusivities for the superior and anterior regions of the corona radiata. Also, a one-way causal relationship was identified for eveningness increasing AD for the superior longitudinal fasciculus (p value $= .027$).

Discussion

This study provides insights into the relation between chronotype and white matter structure. We identified 29 pairwise significant genetic correlations between chronotype and DTI parameters, including MD, AD, RD and MO. Of these, 13 were found to be indicative of a causal relationship. These results show that changes in white matter microstructural organization associated with an evening chronotype are explained by variation in MD, AD, RD and MO tracts.

Recently, there has been a growing interest in the genetic architecture of chronotype and its role in health and disease (García-Marín et al., 2021; Jones et al., 2019). For instance, being a morning person has been proven to be genetically correlated with metabolic traits such as body mass index (BMI), type 2 diabetes and fasting insulin (Jones et al., 2019). Further, phenotypes involving depression, such as *ever had prolonged feelings of sadness or depression* and *ever depressed for a whole week* (García-Marín et al., 2021), have shown negative genetic correlations with morningness, suggesting that individuals leaning toward an evening chronotype share genetic variants with depression phenotypes. In contrast, diseases of the musculoskeletal system and connective tissue have shown a positive genetic correlation with being a morning person (García-Marín et al., 2021).

In the present study, no positive genetic correlations were identified, thus no associations with a tendency to be a morning person are reported. Nonetheless, MD, AD, RD and MO showed significant negative genetic correlations with chronotype. Specifically, negative correlations with chronotype imply that DTI parameters corresponding to white matter structures are correlated with an increase in eveningness. In the present study, the eveningness

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chronotype is associated with higher average MD, AD and RD for all tracts, but with tract-specific distributions for each DTI parameter. Our results are highly consistent with previous findings describing white matter microstructural differences in several brain regions, including the corpus callosum, corona radiata, internal capsule and frontal and temporal lobes, when comparing evening to morning and intermediate chronotypes (Rosenberg et al., 2014).

We identified genetic correlations between an evening chronotype and MD in the entire corpus callosum and corona radiata, as with the posterior segments of the internal capsule. Increased MD may be associated with decreased tissue density, altered properties of the myelin, axonal and neuronal membrane, as well as altered tissue organization and shape of glia and neurons (Sagi et al., 2012; Beaulieu, 2002). Further, in our study, the posterior region of the corona radiata also showed increased RD, but no associations were detected with AD. An increase in AD, but not in RD, was identified in the posterior portion of the internal capsule for the evening chronotype. Similarly, the anterior part of the corona radiata showed genetic correlations between evening chronotype and AD, but not with RD. AD is usually associated with axonal membranes or axonal density (Kumar et al., 2012), while RD is typically associated with myelin density (Kumar et al., 2012). However, both measures could be affected by multiple tissue factors, including the presence of glial tissue, edema or multiple crossing fiber tracts (Winklewski et al., 2018).

Recently, it has been shown that glial cells are involved in the regulation of circadian rhythms and maintenance processes of a healthy brain (Chi-Castañeda & Ortega, 2017), and DTI parameters such as AD and RD can be affected by interactions between neuron and glial cells (Winklewski et al., 2018). We speculate that the role of glial cells in the regulation of circadian rhythms may go further than supporting and participating in metabolic functions. Possibly, abnormalities in glial tissue affecting AD and RD could also contribute to a preference for a morning or evening chronotype and, for *evening* people, increments in AD, RD or both could influence higher MD. However, more research is needed to disentangle the intricate relationship between AD, RD and MD.

Higher MO is associated with a more tubular shape of the diffusion tensor, consistent with the presence of a predominant fiber population. Our results showed that higher MO was associated with a genetic predisposition to the evening chronotype in regions with expected crossing fibers. Although it is expected to observe crossing fibers in superior corona radiata and the retrolenticular portion of the internal capsule, such an increase in MO may be attributed to decreased quality (less densely packed fibers and axonal density) of a portion of the crossing fibers, resulting in a predominant fiber population, also consistent with the increase of AD and MD in the same regions (Concha, 2014; Douaud et al., 2011).

Evening chronotype has been associated with lower sleep quality (Taillard et al., 2003; Vitale et al., 2015), which in turn has been related to increased MD in the hippocampus, basal ganglia, anterior corpus callosum and prefrontal white matter (Khalsa et al., 2017; Takeuchi et al., 2018). Our findings show similar patterns of white matter integrity in evening chronotype and further contribute to identifying an underlying genetic component between chronotype and MD regions. We hypothesize that the relationship between eveningness and higher MD could be mediated by a deficit in sleep quality.

Limitations of the present study must be recognized. Our analyses only used data from participants with European ancestry from the UK Biobank cohort. Since previous studies have pointed out racial differences in circadian rhythms (Egan et al., 2017; Malone et al., 2016), the generalizability of our results may be limited and should be addressed with caution. Furthermore, MR methods rely heavily on the statistical power of the samples, which in turn is tied to the availability of sufficient genetic instruments (i.e., genome-wide significant loci; García-Marín et al., 2021; Pierce et al., 2011). In the present study, individual DTI parameters showed scarce genome-wide significant loci ranging from none to 12, lessening the statistical power of GSMR. Also, MR analyses were performed in the same cohort population (UK Biobank); therefore, the requirement for independent samples could not be met and a possible sample overlap between chronotype and DTI parameters may bias MR estimates (Burgess et al., 2016). Nonetheless, LD score regression is unbiased by sample overlap, thus the estimates for genetic correlations remain unaffected (Bulik-Sullivan, Finucane et al., 2015). Despite reduced statistical power, our findings still provide evidence for causal associations suggesting *eveningness* is causal for increases in mean, axial and radial diffusivities and thus uncover meaningful insights and hypotheses for future studies to confirm when more powerful genetic statistical instruments and techniques become available.

In summary, we provide evidence for 29 genetic correlations between chronotype and brain white matter structure, of which 13 were found to be indicative of a causal relationship. Our results confirmed findings from previous studies and uncovered insights into the relationship between DTI parameters and chronotype. For instance, we reveal that increments in MD in the entire corona radiata and corpus callosum are associated with an evening chronotype. Further, we identified associations between eveningness and increments in the anterior and posterior parts of the corona radiata in RD and AD, respectively. Also, we found the retrolenticular part of the internal capsule to have higher MD, AD and MO among individuals leaning toward an evening chronotype. Altogether, our results contribute to a better understanding of the relationship between the brain and circadian preference.

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Conflict of interest. GC-P contributed to this study while employed at The University of Queensland. He is now an employee of 23andMe Inc., and he may hold stock or stock options. All other authors declare having no conflicts of interest.

Ethical standards. This study was approved by the Human Research Ethics Committee of the QIMR Berghofer Medical Research Institute.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/thg.2021.4.

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