Chronotype, depression and hippocampal volume: Cross-sectional associations from the UK Biobank

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Abstract

Diurnal preference for evening time has been associated with increased odds for current depression and a number of indices of the disorder. In the current study, the association between chronotype and depression was explored in a population-based sample of 5360 adults aged between 40 and 70 years. Previous work has also suggested that larger hippocampal volume may be protective against depression. In an additional, exploratory analysis, hippocampal volume was compared in never-depressed early and late chronotypes (N = 3004). Definite eveningness was significantly associated with increased odds for probable lifetime depression after controlling for a number of confounding factors including neuroticism. Hippocampal volume did not differ between never-depressed early and late chronotypes. The current results extend previous work and add further weight to the argument that late chronotype represents a risk factor for depression.

Keywords:

Chronotype, Depression, Biobank, Hippocampus

1. Introduction

Affecting over 300 million people, Major Depressive Disorder (MDD) is the leading cause of ill health and disability worldwide (WHO, 2017). A better understanding of the factors that contribute to risk for depression and, consequently, the development of preventative strategies is a key research priority.

Increasing evidence suggests that circadian rhythmicity impacts mental health (Fabbian et al., 2016; Kivelä, Papadopoulos, & Antypa, 2018) with eveningness particularly associated with MDD. Recent large, population-based studies in Finnish (Merikanto et al., 2015, 2013) and Dutch adults (Antypa, Vogelzangs, Meesters, Schoevers, & Penninx, 2015) have consistently reported increased odds for a number of markers of depression in evening-types including diagnosis of depression, antidepressant medication and depressive symptoms. Importantly, in these studies increased odds for depression in evening-types was independent of a number of sleep, health and lifestyle behaviours. Previous work (Antypa et al., 2015; Merikanto et al., 2015, 2013), however, has not considered the potential impact of neuroticism, a key vulnerability factor for depression (Chan, Goodwin, & Harmer, 2007; Kendler, Gatz, Gardner, & Pedersen, 2006). The primary aim of the current work, therefore, was to extend earlier findings and determine the association between chronotype and depression in a large sample of United Kingdom (UK) adults while taking into account neuroticism and other relevant sleep, sociodemographic and lifestyle factors.

Investigations of the underlying neuroanatomy of depression have focused on the hippocampus – largely due to its; 1) dense innervation by serotonergic projections from the dorsal raphe, 2) connectivity with regions implicated in emotional processing (e.g. amygdala) and stress response (e.g. hypothalamus), and 3) capacity for neuroplasticity (Palazidou, 2012). A recent large meta-analysis which combined data from 15 studies, comprising over 8900 participants reported small volumetric reductions in bilateral hippocampus of recurrent

depressed patients and those with an early age of onset (≤ 21 years) but not first episode patients (Schmaal et al., 2015). Interestingly, previous work has suggested *larger* hippocampal volume may confer protection against depression in some at-risk groups. For example, Chan and colleagues (Chan et al., 2016) reported greater hippocampal volume in highly neurotic older adults beyond the typical onset age for depression (~32 years of age for MDD, Kessler et al., 2005). For these individuals, who have remained depression free despite possessing a recognised risk-factor for depression (high neuroticism), a larger hippocampal volume may confer protection and therefore represent a resiliency factor against depression. A second, exploratory objective of the current study was to test the hypothesis that older adult moderate and late evening types who had escaped depression would show greater hippocampal volume as compared to more morning types.

2. Methods

Participants

Data were from the UK Biobank, a large, population-based study designed to allow investigation of risk factors for a range of adverse health outcomes in middle and older age adults (Sudlow et al., 2015). The UK Biobank is an open access resource with data collected from over 500,000 community-dwelling individuals aged between 40 and 69 years. Baseline assessment was conducted between March 2006 and October 2010 using identical assessment procedures across 22 assessment centres located throughout the UK. Ethical approval to the UK Biobank was granted by the NHS National Research Ethics Service North West (Reference number: 11/NW/0382). The current study was approved by the UK Biobank Access Committee (Project reference number 30833).

Measures

The principal exposure variable was chronotype which was assessed in the Biobank cohort with the single question: "Do you consider yourself to be definitely a morning person/more a morning than an evening person/more an evening than a morning person/definitely an evening person". This question is similar to the final question of the full and reduced versions of the Morningness-Eveningness Questionnaire ("One hears about "morning types" and "evening types". Which one of these types do you consider yourself to be?" Horne & Östberg, 1976).

Current and previous depressive symptoms were assessed using items relating to lifetime experience of depression, items from the Patient Health Questionnaire (PHQ) and items on help-seeking for mental health (Smith et al., 2013; Spitzer, Kroenke, & Williams, 1999). By this instrument participants were categorised as: Recurrent major depression (severe); Recurrent major depression (moderate); Single episode major depression; No mood disorder. Participants with a probable bipolar disorder or those that did not provide a response were excluded.

Covariates in the model were selected based on the potential to confound associations between chronotype and depression. These included age, sex, alcohol-use, smoking status, socioeconomic status, education, sleep duration and neuroticism. Sex and ethnicity were identified by self-report. Smoking status was determined according to the following categories: "never"; "previous", "current" or "prefer not to answer". Socioeconomic status was based on the Townsend Deprivation Scale with each participant assigned a score based on their post code at enrolment (Townsend, 1987). Education attainment was determined with the following categories: "College/University degree", "A/AS level or equivalent", "O Level/GCSE or equivalent", "CSE or equivalent, NVQ/HNC/HND or equivalent", "Other professional qualification (e.g. nurse or teacher)", "None of the above", "Prefer not to say". Sleep duration

was determined using the question "About how many hours sleep do you get in every 24 hours (please include naps)?" with values provided as integers. Neuroticism summary score was based on 12 neurotic behaviour domains with scores ranging from 0 -12 (higher scores indicating greater neuroticism, Eysenck, Eysenck, & Barrett, 1984). Alcohol intake frequency was determined by self-report with the following categories: "Daily or almost daily", "Three to four times a week", "Once or twice a week", "One to three times a month"," Special occasions only", "Never", and "Prefer not to answer".

Brain imaging acquisition parameters and processing

T_1-weighted anatomical images for each participant were acquired on a single Siemens Skyra 3T scanner (Siemens, Erlangen, Germany) fitted with a 32-channel head coil according to previously reported procedures (Alfaro-Almagro et al., 2017; Miller et al., 2016) with online documentation available here: http://biobank.ctsu.ox.ac.uk/crystal/docs/brain_mri.pdf. All image preprocessing was conducted by the Biobank neuroimaging team and included non-brain removal, bias-field correction and tissue segmentation. Further processing included subcortical segmentation to yield volumes for 15 structures (see http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST/UserGuide) including left and right hippocampus. Intracranial volume (ICV) was estimated as the inverse of the determinant of the rotation-translation matrix obtained after affine registration to a standard template multiplied by the template volume and used to correct for differences in head size (here referred to as normalised volume). Complete data (T_1-weighted anatomical image plus measures and covariates described above) were available for 3004 participants categorised as no mood disorder (please see Table 3).

Statistical treatment

Chronotype and Depression: Analyses were restricted to participants with complete data on the main exposure variable (chronotype) and depression status and further excluded those missing any covariate data yielding a final data sample size of N = 5360 with complete data sets. Chronotype groups (definitely morning (DM), more morning than evening (MM), more evening than morning (ME) and definitely evening (DE) were compared using analyses of variance (ANOVA) for continuous variables (e.g. age) and chi-square test for categorical variables (e.g. sex). Prevalence of depression (dichotomised as probable major depression/no mood disorder) between groups was also compared after adjustment for the covariates listed above using logistic regression.

Hippocampal volume: To explore resilience, hippocampal volume (N = 3004) was investigated using Analysis of Variance (ANOVA) with chronotype as the between-subjects factor after adjustment for age, sex, alcohol use, smoking status, socioeconomic status, education, sleep duration and neuroticism. The probability of $p < .05$ was set as the accepted level of significance and all statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) v25 (IBM, New York, USA).

3. Results

Across the entire sample (N = 5360) ages ranged from 40 to 70 years (M = 55.71, SD = 7.46) and 51.3% were females (please see Table 1 for a description of the full sample and stratified by chronotype). Definitely morning types (DM) made up 25.8% of the sample, MM 37.9%, ME 28.0% and DE 8.4% - a distribution similar to previous studies using the Biobank sample (Knutson & von Schantz, 2018; Kyle et al., 2017). The no mood disorder group comprised 70.1%, 8.1% of included participants satisfied criteria for a probable single lifetime

episode of major depression, 14.3% for probable recurrent major depression (moderate) and 6.6% for probable recurrent major depression (severe).

Participants who identified as DE or ME included a higher proportion current smokers. A larger proportion of DE individuals drank 1-3 times a month with the reverse true for DM types. Participants who identified as DM were on average older and less neurotic than the other chronotype groups and slept fewer hours than MM individuals (Table 1). Definite evening type was associated with a higher prevalence of severe and moderate depression. Odds ratios for depression based on chronotype after adjusting for age, sex, smoking status, socioeconomic status, sleep duration and neuroticism are shown in Table 2. Definite evening types were significantly more likely to report depression as compared to DM types (odds ratio (OR) 1.51, 95% CI 1.09, 2.08, p = .01). No significant interactions by sex were observed.

Exploratory analysis

When comparing never-depressed participants, individuals who identified as DM or ME included a higher proportion current smokers than MM or DE. Definite morning types were older than ME and DE types. Definite morning participants had lower neuroticism scores than ME and DE and slept fewer hours than MM types (Table 3). Normalised hippocampal volumes did not differ as a function of chronotype (Left hippocampus: DM, M = 0.002756, SD = 0.00034; MM, M = 0.002759, SD = 0.00033, ME M = 0.002764, SD = 0.00032, DE M = 0.002763, SD = 0.00033, $F(3,2991) < 1$: Right hippocampus: DM, M = 0.002820, SD = 0.000345; MM, M = 0.002836, SD = 0.000335, ME M = 0.002849, SD = 0.000336, DE M = 0.002832, SD = 0.0003383, $F(3,2991) < 1$).

Table 1. Participant characteristics, full sample and stratifed by chronotype

	Full sample	DM	MM	ME	DE
N (%)	5360	1380 (25.8)	2033 (37.9)	1499 (28.0)	448 (8.4)
Female (%)	51.3	51.8	52.8	48.6	52
Age (years, *M* (SD))##	55.71 (7.46)	56.51(7.21)	55.82 (7.34)	55.12 (7.71)	54.69 (7.52)
Age range (years)	40-70	40 - 70	40 - 70	40 - 70	40 - 70
Education (%):					
College/University	45.7	44.6	47.3	43.2	52.0
A level/AS level	13.7	12.5	13.7	14.6	14.3
O level/GCSE	19.9	19.3	19.2	21.2	20.1
CSE/Equivalent	4.1	4.4	3.8	4.5	3.1
NVQ/HND	5.8	5.9	5.8	6.1	4.7
Other professional	5	5.7	4.8	5.1	3.3
None of the above	5.8	7.5	5.3	5.3	4.2
Smoking (%):**					
Never	62.3	62.8	63.9	61.1	58.0
Previous	32.1	32.8	31.9	30.2	32.8
Current	5.6	4.5	4.2	24.8	9.2
Alcohol consumption (%)*					
Daily/Almost daily	21.3	21.3	20.0	23.2	20.1
3-4 times per week	29.3	28.5	29.6	30.2	28.1
Once a week	25.1	26.5	25.1	24.8	22.1
1-3 times per month	11.2	9.2	12.1	10.3	16.1
Special occasions only	8.4	8.8	8.6	7.7	8.3
Never	4.7	5.7	4.5	3.9	5.4
How many hours sleep do you get in every 24 hour period (including naps) Hours (*M* (SD))#	7.19 (.96)	7.13 (1.0)	7.23 (.93)	7.22 (.96)	7.13 (.95)
Neuroticism (M (SD))##	3.74 (3.1)	3.39 (2.97)	3.68 (3.0)	3.91 (3.19)	4.48 (3.4)
Depression (%)					
No mood disorder	70.1	72.4	70.7	70.4	60.9
Probable recurrent severe depression	6.6	5.4	6.0	6.7	12.5
Probable recurrent moderate depression	14.3	13.3	14.3	13.9	19.2
Single probable major depression	8.1	8.0	8.0	8.1	8.3

Chi-square tests, $p < .001$**; $p = .005$*/ANOVA, $p < .001$##; $p = .01$#

Table 2. Association between chronotype and depression. Abbreviations as in the text. DM as referent.

	DM	MM	ME	DE
Depression OR (95% CI)	Reference	.97 (.78,1.2)	.936 (.74,1.18)	1.51 (1.09,2.08)
		p .76	*p* .96	*p* .01

Table 3. Participant characteristics, never-depressed sample stratifed by chronotype

	Full sample	DM	MM	ME	DE
N (%)	3004	792 (26.4)	1164 (38.7)	839 (27.9)	209 (7.0)
Female (%)	47.9	48.6	49.1	46.6	44.0
Age (years, *M* (SD))###	56.041 (7.43)	56.87 (7.32)	56.04 (7.21)	55.52 (7.81)	55.00 (7.64)
Age range (years)	40-70	40-70	40-70	40-70	40-69
Education (%):					
College/University	46.1	44.7	47.9	43.5	51.2
A level/AS level	13.7	12.6	13.6	14.7	14.4
O level/GCSE	19.3	19.2	18.1	21.1	19.6
CSE/Equivalent	3.7	3.3	3.6	4.5	1.4
NVQ/HND	5.9	6.2	5.8	6.0	5.3
Other professional	5.2	5.8	5.3	4.9	2.9
None of the above	6.2	8	5.7	4.9	5..3
Smoking (%):*					
Never	64.7	64.0	67.4	63.5	57.9
Previous	30.3	32.2	28.6	30.0	34.0
Current	4.9	3.8	4.0	6.4	8.1
Alcohol consumption (%)					
Daily/Almost daily	21.7	21.8	21.3	22.8	19.6
3-4 times per week	30.5	30.4	30.2	30.6	31.6
Once a week	26.2	27.3	25.3	26.9	23.9
1-3 times per month	10.2	7.7	11.8	9.4	13.9
Special occasions only	7.8	8.0	7.6	7.6	8.6
Never	3.7	4.8	3.9	2.6	2.4
How many hours sleep do you get in every 24 hour period (including naps) Hours (*M* (SD))#	7.21 (.93)	7.14 (.98)	7.25 (.92)	7.25 (.90)	7.16 (.88)
Neuroticism (M (SD))##	3.11 (2.80)	2.8 (2.68)	3.13 (2.75)	3.26 (2.91)	3.50 (3.01)

Chi-square tests, $p < .006$*; ANOVA, $p < .001$###; $p = .001$##; $p = .03$#

Discussion

Definite eveningness was associated with increased prevalence of probable lifetime MDD. There was no evidence that the association between definite eveningness and depression differed between men and women. Within the no mood disorder group, hippocampal volume was not impacted by chronotype. The current findings extend previous work delineating a link between chronotype and depression to a large UK sample adjusted for neuroticism – a widely reported risk-factor for depression.

A strength of this study is the relatively large sample size. Limitations, which should be taken into consideration when interpreting the results, include the use of a single question to assess chronotype. However, this is very similar to the final question of the full and reduced versions of the Morningness-Eveningness Questionnaire ("One hears about “morning types” and “evening types.” Which one of these types do you consider yourself to be?" Adan & Almirall, 1991; Horne & Östberg, 1976) which correlates strongly with total rMEQ score (r = .89, Adan & Almirall, 1991). Also, lifetime estimates for depression, although comparable with other population lifetime estimates (Smith et al., 2013), were based on self-report of symptoms rather than formal diagnosis. The prevalence estimates reported here, therefore, are for probable lifetime diagnosis rather than actual diagnosis. Further, temporality cannot be inferred from the current study and the reported association between chronotype and depression does not indicate causality. A number of chronic diseases that have been associated with chronotype (e.g. cardiovascular disease) were not assessed and so a potential impact of such diseases on the current results cannot be excluded. Finally, the UK

Biobank cohort has been reported to be generally healthier than the general population (Fry et al., 2017). The current findings may, therefore, not generalise to the entire population.

Increasing evidence indicates an association between late chronotype and psychological health – particularly depression. For example, in a large (n = 6071) population sample from Finland Merikanto and colleagues (Merikanto et al., 2013) reported that late chronotypes, after adjustment for sex, age, education and smoking status, were significantly more likely to report depressive symptoms, diagnosis of depression or use of prescribed antidepressant medication (ORs, respectively, 3.01, 3.82, 2.72). Intermediate type, relative to morning type, was also associated with depression although to a lesser degree (ORs, respectively, 1.56, 1.54, 1.60). In a second larger sample (n = 10503) that combined data from two studies the same group observed similar, albeit more modest, effects after controlling for sex, age, education, socioeconomic status, alcohol consumption, smoking status and sleep (depressive symptoms, OR (evening type vs morning type) 2.2, diagnosis of depression OR 2.9, antidepressant medication, OR 2.1, Merikanto et al., 2015). In a Dutch sample (n =1944) that included currently depressed and/or anxious patients, remitted depressed and healthy controls Antypa and colleagues (2016) reported an association between current depression and late chronotype but not dysthymia (persistent mild depression) or anxiety after controlling for a number of clinical, sleep and somatic health factors (Antypa et al., 2015). Previous work, from large population studies, shows good consensus and strong evidence for an association between late chronotype and depression after controlling for a number of clinical, lifestyle and health related factors (Antypa et al., 2015; Merikanto et al., 2015, 2013). The current work adds to this corpus and extends previous findings to a large UK adult sample which included a measure of neuroticism – a personality trait widely reported as a vulnerability factor for psychopathology (Chan, Goodwin, & Harmer, 2007).

The mechanisms that link eveningness and depression likely arise from multiple sources and interactions. Evening-types are more prone to circadian misalignment of biological rhythms as society dictates work schedules that are generally more aligned to individuals with a more morning profile. This misalignment, often referred to as "social jetlag" has been proposed as a link between eveningness and depression and other more general health hazards (e.g. cardiovascular disease, diabetes; Merikanto et al., 2015). However, Knapen and colleagues (Knapen et al., 2018) found no difference between depressed patients and a matched sample of healthy controls in the degree of social jetlag or evidence for an association between depressive symptomatology and circadian misalignment.

In addition to circadian misalignment, eveningness is also associated with a higher prevalence of sleep problems (Merikanto et al., 2012) and sleep disorders show widespread comorbidity with established psychiatric disorder (Sheaves et al., 2016). However, the current results and previous work suggest evening types are at increased odds for depression independent of sleep quality or sufficiency. Indeed, Horne *et al.*, (2018) reported that eveningness was associated with increased depressive symptoms and mediation analysis showed that this relationship was only partly mediated by sleep quality (Horne, Watts, & Norbury, 2018) . Current evidence, therefore, suggests that indicators of depression observed in evening-type individuals cannot be attributed exclusively to disturbed sleep.

Behaviourally, evening type has been associated with a number of traits and cognitions that may, in part, explain the link between chronotype and depression. For example, eveningness has been associated with maladaptive emotion regulation strategies (increased expressive suppression and reduced cognitive reappraisal) after controlling for age, gender, depressive symptomatology, neuroticism, and sleep quality (Watts & Norbury, 2017). Antypa *et al.*, observed that eveningness was associated with increased cognitive reactivity (i.e. the tendency to activate negative thoughts when mood is low) and rumination

(repetitive negative thinking) (Antypa et al., 2017). Eveningness is also associated with increased recognition of sad facial expressions, greater recall and reduced latency to correctly recognise previously presented negative personality trait words, and reduced allocation of attentional resources to happy faces in late chronotypes (Berdynaj et al., 2016). Similarly, Horne *et al.*, (Horne, Marr-Phillips, Jawaid, Gibson, & Norbury, 2017) reported increased recognition accuracy in late chronotypes for sad compared with happy faces independent of sleep quality, mood, age, and gender. Trait rumination, expressive suppression, reduced cognitive reappraisal and negative biases in emotional processing are known to increase depression risk (Aldao, Nolen-Hoeksema, & Schweizer, 2010). Interventions that target these malleable, negative cognitions in evening type individuals prior to the onset of depression may delay or prevent onset in this at-risk group and increase our understanding of the association between chronotype and depression.

A number of studies have reported volumetric differences between depressed patients and healthy controls in a number of subcortical regions - particularly the hippocampus (Schmaal et al., 2015). Apposite to the current study, previous work in older adult at-risk groups (highly neurotic) has suggested that larger hippocampal volumes may confer protection against depression (Chan et al., 2016**)**. The relative older age of the current never-depressed sample (*M* = 56 years) allowed a similar analytical approach. Accepting late chronotype as a risk factor for depression, the moderate and definitely evening types with no probable lifetime mood disorder may represent a resilient group. That is, these individuals through virtue of being later chronotype, possess a vulnerability phenotype but have not suffered with depression to an age beyond typical onset for this disorder. However, there was no evidence of greater hippocampal volume in probable never-depressed evening-type participants (either moderate or definite) as compared to never-depressed morning-types. It is

possible, therefore, that hippocampal volume is an important mediator of risk and resilience in highly neurotic individuals but this is not relevant to chronotype.

In conclusion, the current work extends previous findings and demonstrates that eveningness is associated with increased odds for depression after adjustment for a number of health, sociodemographic, lifestyle and personality traits (neuroticism). Further research to better our understanding of the mechanisms that link chronotype and depression is warranted and could lead to the development of strategies to mitigate the increased risk for depression associated with being an evening-type.

Conflict of interest

There author reports no conflicts of interest.

Funding

This research was supported by a small research grant from the University of Roehampton.

Acknowledgements

The author is grateful to all the participants who contributed to this research and to the Medical Research Council UK Biobank for generating such a valuable resource.

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Supplemental Table 1.

Supplemental Table 1. Participant characteristics in never-depressed with brain scan and never-depressed no scan

	Included	Excluded	*p*
N	3004	747	
Female (%)	47.9	43.8	0.04*
Age (M (SD))	56.1 (7.44)	56.61 (7.43)	0.06
TDI (M (SD))	-2.32 (2.41)	-2.22 (2.54)	0.35
How many hours sleep do you get in every 24 hour period (including naps) Hours (*M* (SD))	7.21 (.93)	7.16 (.96)	0.18
Neuroticism (M (SD))	3.11 (2.8)	2.92 (2.6)	0.09
Smoking (%):			
Never	64.7	62.8	
Previous	30.3	31.9	0.6
Current	4.9	5.4	
Alcohol consumption (%)*			
Daily/Almost daily	21.7	22.5	
3-4 times per week	30.5	28	
Once a week	26.2	23.3	0.043*
1-3 times per month	10.2	12	
Special occasions only	7.8	8.6	
Never	3.7	5.6	
Education (%):			
College/University	46.1	45.6	
A level/AS level	13.7	14.1	
O level/GCSE	19.3	18.78	
CSE/Equivalent	3.7	4.8	0.87
NVQ/HND	5.9	5.5	
Other professional	5.2	4.8	
None of the above	6.2	6.4	
Chronotype (%):			
DM	26.4	27.3	
MM	38.7	36.4	0.67
ME	27.9	28.6	
DE	7	7.6	

Chi-square tests*

Never-depressed participants that provided a T_1 anatomical scan were compared to never-depressed with no brain scan. Continuous variables (e.g. age) were compared using independent samples *t*-tests and chi-square test for categorical variables (e.g. sex). TDI =

Townsed Deprivation Index, DM/MM/ME/DE = Definite Morning/More Morning/More Eveing/Definite Evening type.