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Journal:	*Chronobiology International*
Manuscript ID	LCBI-2018-0055
Manuscript Type:	Short Communications
Date Submitted by the Author:	07-Mar-2018
Complete List of Authors:	Horne, Charlotte; University of Roehampton, Psychology Norbury, Ray; University of Roehampton, Psychology
Keywords:	Chronotype, Hippocampus, Emotion, Depression, Emotion regulation, Morphology

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Exploring the effect of chronotype on hippocampal volume

and shape: A combined approach.

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Abstract

Current evidence suggests that acute depression is associated with reduced total hippocampal volume and regional atrophy. Here, using structural magnetic resonance imaging, we assayed linear effects of chronotype on total hippocampal volume and morphology. Later chronotype was associated with localised atrophy in the subiculum region of the right hippocampus in the absence of changes in total volume. The hippocampus forms a key node in a network of brain regions implicated in emotional regulation and alterations in the structure of this region may underpin, in part, the increased vulnerability for depression in late chronotype individuals.

Keywords: Chronotype, Hippocampus, Emotion, Depression, Regulation, Morphology

Total word count: 4180 (including table and figure legends)

Abstract word count: 94

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Introduction

Major Depressive Disorder (MDD) is one of the most prevalent and debilitating of all psychiatric disorders, affecting 4-17% of the general population (Wong & Licinio, 2001). Fewer than half of patients reach remission with standard pharmacotherapy and nearly 80% of patients suffer relapse. Often starting in adolescence (Kessler, Avenevoli, & Ries Merikangas, 2001), MDD follows a chronic course with a high risk of recurrence or persistence into adulthood and is associated with ongoing psychosocial difficulties and elevated risk for general medical illness (Nicholson, Kuper, & Hemingway, 2006). This malignant pattern of psychosocial dysfunction and disability suggests that the most effective strategies to reduce the health burden of MDD would be obtained through the targeting of 'at-risk' individuals.

A number of risk factors for depression have been identified including positive family history (Wells, Deykin, & Klerman, 1985), female gender (Piccinelli & Wilkinson, 2000), neuroticism (Vittengl, 2017) and childhood abuse (Widom, DuMont, & Czaja, 2007). Increasing evidence also identifies late chronotype as a vulnerability factor for depression (Fabbian et al., 2016). Across the general population late chronotype is associated with increased depressive symptomatology (Levandovski et al., 2011; Merikanto et al., 2013, 2015; Togo, Yoshizaki, & Komatsu, 2017), diagnosis of depression and use of antidepressant medication (Merikanto et al., 2013, 2015). Together, these data demonstrate a clear association between late chronotype and depression but the observational nature of these studies prevents examination of the underlying mechanisms that confer risk.

In the context of depression, one structure that has received significant critical inspection is the hippocampus (Rogers, Renoir, & Hannan, 2017). For example, the hippocampus is densely innervated by 5-HT (serotonin) projections from the dorsal raphe. Serotoninergic signalling is strongly implicated in a number of psychiatric disorders

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including depression and plays a key role in the cognitive and emotional processing that underlies them. The hippocampus is highly connected to other subcortical regions involved in emotional processing (e.g. amygdala) and also the hypothalamus (which forms part of the stress-related hypothalamic-adrenal-pituitary axis (HPA axis)). Moreover, it has been demonstrated that functionally relevant levels of neurogenesis occur in the adult human hippocampus (Spalding et al., 2013) and adult hippocampal neurogenesis is implicated in antidepressant response, stress response and cognitive function (O'Leary & Cryan, 2014).

Due to the implicated role of the hippocampus in medication response, stress and cognition, a large number of Magnetic Resonance Imaging (MRI) studies have investigated hippocampal volume in MDD. Although equivocal (Bora, Fornito, Pantelis, & Yücel, 2012), a number of meta-analyses indicate reductions in hippocampal volume in patients *vs.* controls (Arnone, McIntosh, Ebmeier, Munafò, & Anderson, 2012; MacQueen et al., 2003; Schmaal et al., 2015). It is unclear, however, if these reductions are an outcome of the onset of clinical symptoms (i.e. the neurotoxicity hypothesis (Sheline, 2011)) or predate the onset of the disorder (i.e. the vulnerability hypothesis (Baaré et al., 2010; Durmusoglu et al., 2018)). Support for the vulnerability hypothesis can be found across a number of studies that have demonstrated reduced hippocampal volume and/or shape differences in euthymic participants with positive family history for depression (Baaré et al., 2010; Chen, Hamilton, & Gotlib, 2010; Durmusoglu et al., 2018) and early-life adversity (Dahmen et al., 2017) – two well recognised risk factors for depression. To our best knowledge, however, no one has yet investigated hippocampal volume or shape and related this to chronotype. Based on the extant literature and consistent with the vulnerability hypothesis, we predicted that later chronotype would be associated with lower total hippocampal (volumetric analysis) and localised atrophy (vertex analysis).

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Methods

Participants

The study was approved by the local ethics committee and written informed consent

was obtained prior to any study procedures taking place. A total of 50 participants were

recruited, all were in good physical health and free of concurrent medication. Exclusion

criteria were current or previous depression, presence of major depression in a biological

parent, diagnosed sleep disorder (each assessed by self-report) and contraindication for MR

examination. Chronotype, sleep quality and depression/anxiety were determined using,

respectively, the 5-item reduced Morningness-Eveningness Questionnaire (Adan & Almirall,

1991) the Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer,

1989). and the Patient Health Questionniare-4 (Löwe et al., 2010). Please see Table 1 for

details.

TABLE 1 NEAR HERE PLEASE

Image data acquisition

All imaging data were acquired on a research dedicated 3T Magnetom TIM Trio

(Siemens, Erlangen, Germany) fitted with a 32-channel head coil and located at the

Combined Universities Brain Imaging Centre (CUBIC). For each participant, we collected a

T_1-weighted whole-brain scan (magnetization-prepared rapid acquisition with gradient echo

(MPRAGE), inversion time (TI) = 1100 ms, repetition time (TR) = 1830 ms, echo time

(TE) = 3.03 ms, flip angle (FA) = 11°, field of view (FOV) = 256 × 256 × 160 mm³, voxel

size = 1 × 1 × 1 mm³).

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Data analysis pipeline

All image pre-processing and analyses were performed using FSL version 5.0.10

(FMRIB Software Library, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Non-brain removal was

performed on each individual's T_1-weighted image using a deformable model that evolves to

fit the brain's surface by the application of a set of locally adaptive model forces. Subcortical

brain measures (bilateral hippocampus) were delineated using FMRIB's Integration

Registration and Segmentation Tool (FIRST). FIRST is a model-based segmentation tool that

utilises shape and appearance models taken from an atlas of manually segmented images

from the Centre for Morphometric Analysis. These manual segmentations are parameterised

as surface meshes from which a point distribution is modelled. Using the observed intensities

from each individual's T_1-weighted image FIRST finds the most probable shape by searching

through linear combinations of shape variation modes resulting in a hippocampus

segmentation for each individual in native space. At each step, processed images were

carefully inspected by one of the authors (CH) to ensure accuracy of results. 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.

In addition to volumetric analyses, vertex analyses were also conducted to investigate

localised shape differences in the hippocampus. Based on the segmentation described above

the boundary for each structure (left and right hippocampus) were reconstructed into a vertex-

based surface and the vertex locations for each subject projected on the surfaces of the

average shape transformed to Montreal Neurological Institute space. The projections were

scalar values representing the signed, perpendicular distance from the average surface, where

negative/positive values indicate, respectively, greater inversion/eversion from the average

hippocampal shape. Linear effects of chronotype on scalar projection values were tested for

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significance using non-parametric permutation tests (applying 5000 permutations) with sleep

quality, age, gender and mood/anxiety included as covariates in the regression model. Control

of the family-wise error rate was obtained using cluster-based thresholding with an initial

threshold of $Z > 3.1$ and a corrected spatial extent threshold of $p = .05$.

Results

Right and left hippocampal volumes as percentage of ICV ($M = .00265$, SD .0004; M

$= .00262$, SD .0004) were similar to previously published findings (Dean et al., 2016). There

were no laterality effects (dependent samples $t(49) = .693$, $p = .49$) or association with rMEQ

(right: $r(50) = .085$, $p = .56$; left $r(50) = .060$, $p = .69$). Vertex analyses showed a significant

relationship between vertex height and chronotype such that increased inversion (atrophy)

was associated with later chronotype in a mid-anterior region of the right hippocampus

(please see Figure 1). There was no relationship between localised shape change and

chronotype in left hippocampus.

FIGURE 1 NEAR HERE PLEASE

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Discussion

The principle aims of the current work were to investigate hippocampal volume and shape in never-depressed healthy participants and relate this to chronotype. Consistent with our original hypotheses later chronotype was associated with localised atrophy in right hippocampus independent of age, gender sleep quality and mood. However, contrary to our predictions, there was no relationship between total hippocampal volume and chronotype.

Interpretation of the current findings should take into consideration a number of limitations. Current, previous and family history of depression was determined using self-report. Future studies may benefit from reference to medical history or structured clinical interview to assess exclusion criteria. We also did not measure or exclude participants with high neuroticism which is another population proven to be at-risk of depression (Kendler, Gatz, Gardner, & Pedersen, 2006). However, previous work suggests that, in the age range included in this study, neuroticism does not impact on hippocampal volume (Chan et al., 2016). Of note, repeated clinical observations have reported an association between acute depression and increased availability of cortisol. The hippocampus is enriched with glucocorticoid receptors and elevated cortisol secretion is associated with reduced neurogenesis and neurotoxicity (Cowen, 2010). We did not measure cortisol levels in our participants so cannot exclude a potential impact of this hormone on our findings. Arguing against this however, a number of studies have reported increased cortisol waking response and higher overall concentrations of cortisol in early *vs.* late chronotypes (Kudielka, Federenko, Hellhammer, & Wüst, 2006; Maierova et al., 2016). In respect to risk for depression, an elevated waking cortisol response has been reported in some groups at risk for depression (e.g. positive family history, Mannie, Harmer, & Cowen, 2007) but not others (e.g high neuroticism, Chan, Harmer, Goodwin, & Norbury, 2008). As we excluded participants with a positive family history of depression and current, although limited, evidence suggests

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early chronotype is associated with higher levels of cortisol we would argue that fluctuation in cortisol levels is an unlikely explanation for our findings.

Current evidence indicates the acute depression is associated with modest reductions in total hippocampal volume (Arnone et al., 2012; MacQueen et al., 2003; Schmaal et al., 2015). The temporal characteristics of these changes, however, are not fully understood. The neurotoxicity hypothesis posits that volumetric changes are a neurodegenerative response to chronic stress (Sheline, 2011). The biological abnormalities underlying this volume reduction are likely multifactorial, including prolonged exposure to glucocorticoids and stress-induced reductions in neurotrophic factors and neurogenesis. In support of the neurotoxicity hypothesis a number of studies have reported that cumulative duration of lifetime depression, number of depressive episodes and an earlier age of depression onset are associated with hippocampal volume loss (MacQueen et al., 2003; Sheline, Sanghavi, Mintun, & Gado, 1999).

Hippocampal volume reduction has also been reported in groups at increased risk for depression. For example, Chen and colleagues (2010) observed reduced hippocampal volume in adolescent daughters of mothers with recurrent episodes of depression that occurred during the daughter's lifetime (at-risk group) as compared with age-matched daughters of mothers with no history of depression. Similarly, Amico *et al.*, (2011) compared hippocampal volume in currently depressed, at-risk (family history of depression) and control adults (Amico et al., 2011). The high-risk group had smaller right hippocampal volume than the depressed and low-risk group (high-risk < depressed < low-risk) a finding that may be consistent with plasticity effects of antidepressant treatment (O'Leary & Cryan, 2014). Of note, Chan and colleagues (Chan et al., 2016) compared hippocampal volume in older adult highly neurotic individuals (another established risk factor depression), recovered depressed patients and age-matched low neuroticism controls. They reported larger bilateral hippocampal volumes in the

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at-risk group as compared to the recovered depressed and low neuroticism groups. The

authors concluded that the larger hippocampal volume in this older adult (mean age 40 years)

at-risk group may reflect a resilience factor. In a complimentary study the same authors

compared high and low neurotic younger adults (mean age 20 years) and found no

differences in hippocampal volume (Chan et al., 2016).

We did not observe an association between later chronotypes and global hippocampal

volume. We did, however, observe more subtle localised atrophy related to chronotype in a

mid-anterior region of the right hippocampus. Indeed, a number of studies in depressed

patients have revealed localised shape changes in the absence of global reductions in volume.

For example, Isikli *et al*., (2013) reported bilateral hippocampal shape alterations in currently

depressed patients as compared to a matched group of healthy controls in a number of regions

including an area on the inferior surface of the right hippocampus (subiculum) similar to that

reported here.   Similarly, Posener and colleagues, using high dimensional mapping of the

hippocampus, reported inward deformations in the right subiculum of currently depressed

patients (Posener et al., 2003). Bearden *et al*., (2009) observed that more severe symptom

severity in unmedicated currently depressed patients was associated with greater left

hippocampal atrophy in Cornu Ammonis (CA) 1 and subiculum (Bearden et al., 2009). More

recently, Watanabe and colleagues (Watanabe et al., 2017) reported significant inward

deformations in bilateral CA 1 and subiculum in first episode drug-naïve depressed patients

as compared to a demographically similar helahty control group. In addition, within the

patient group there was a linear relationship between the degree of deformation and serum

cortisol levels.

The above findings suggest that localised hippocampal atrophy, particularly in CA1

and subiculum, is present during the acutely depressed state. Data on whether these

morphological changes are present prior to the onset of disease (vulnerability factor) are more

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limited.   In support of the vulnerability hypothesis Durmusoglu and colleagues reported

contractions in the right CA1/subiculum border in young adult women at increased risk for

depression by virtue of a mother with a diagnosis of recurrent depression (Durmusoglu et al.,

2018). These data are similar to our own findings and provide further evidence that in some

vulnerable individuals localised hippocampal atrophy precedes the onset of depression and,

therefore, may be implicated in the aetiology of the disorder.

The trajectory and functional significance of the localised atrophy reported here are

unknown. It is possible that the extent and degree of atrophy increases over time with the

accumulation of atrophy ultimately leading to clinical depression. In addition, the

hippocampus is critically involved with emotion regulation (Amico et al., 2011) and projects

to a number of limbic regions including the amygdala. Here we did not measure emotion

regulation directly but previous work suggests that later chronotype is associated with

maladaptive emotion regulation strategies (reduced cognitive reappraisal and increased

emotion suppression, Watts & Norbury, 2017) and greater rumination and cognitive

reactivity (Antypa et al., 2017). Moreover, late chronotype has been associated with reduced

microstructural integrity in the white matter underlying the left anterior cingulate cortex

(ACC; Rosenberg, Maximov, Reske, Grinberg, & Shah, 2014) and an elevated amygdala

response to negative emotional stimuli and reduced amygdala-ACC functional connectivity

(Horne & Norbury, 2018). Together, these regions form key nodes in a network of brain areas

implicated in emotional regulation (Hiser & Koenigs, 2017) and alterations in the structure

and function of these regions may underpin, in part, the increased vulnerability for depression

in late chronotype individuals. Future, well-powered, prospective studies are required to

investigate and better understand the importance of the structural and functional changes

reported here and elsewhere (Rosenberg et al., 2014) for the development of depression in

late chronotype individuals.

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Variable	*M* (SD)	Range (this sample)	Range (original scale)
Age	21.24 (3.77)	18-37	-
Gender	Female 38 (76%); Male 12 (24%)	-	-
Sleep quality	7.30 (3.42)	1 - 15	0 – 21
Chronotype	12.62 (3.62)	6 - 20	4 – 25
PHQ-4 (Anxiety)	0.91 (1.09)	0 - 5	0 – 6
PHQ-4 (Mood)	1.61 (1.58)	0 - 6	0 -6

Table 1. Basic demographics, sleep quality (PSQI), chronotype (rMEQ), mood and anxiety (PHQ-4). Please see Methods for questionnaire details. Values show mean (SD). Also included are the questionnaire range (minimum-maximum) for the study sample and original scale.
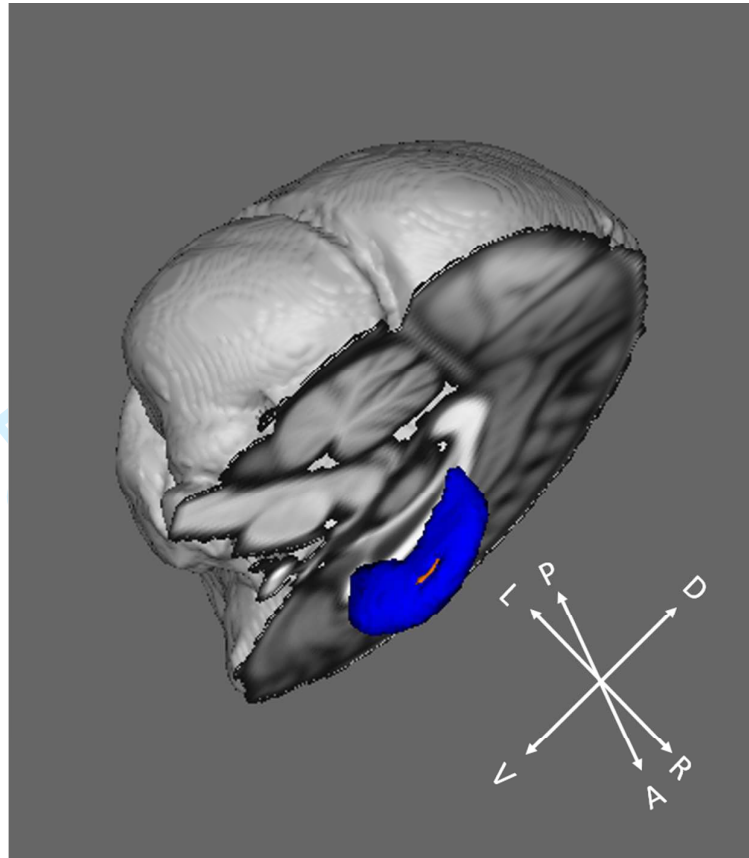
Figure 1. Vertex analysis shows focal atrophy (shown in red) associated with later chronotype

on the ventral aspect of the mid-anterior right hippocampus. V,D,L,R,P,A; ventral, dorsal,

left, right, posterior, anterior.