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## Research Report

# Circadian modulation of memory and plasticity gene products in a diurnal species

Carmel A. Martin-Fairey<sup>a</sup>, Antonio A. Nunez<sup>a,b,\*</sup><sup>a</sup>Department of Psychology, Michigan State University, East Lansing, MI 48824, USA<sup>b</sup>Neuroscience Program, Michigan State University, East Lansing, MI 48824, USA

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## ABSTRACT

Cognition is modulated by circadian rhythms, in both nocturnal and diurnal species. Rhythms of clock gene expression occur in brain regions that are outside the master circadian oscillator of the suprachiasmatic nucleus and that control cognitive functions, perhaps by regulating the expression neural-plasticity genes such as brain derived neurotrophic factor (BDNF) and its high affinity receptor, tyrosine kinase B (TrkB). In the diurnal grass rat (*Arvicanthis niloticus*), the hippocampus shows rhythms of clock genes that are 180° out of phase with those of nocturnal rodents. Here, we examined the hypothesis that this reversal extends to the optimal phase for learning a hippocampal-dependent task and to the phase of hippocampal rhythms in BDNF/TrkB expression. We used the Morris water maze (MWM) to test for time of day differences in reference memory and monitored daily patterns of hippocampal BDNF/TrkB expression in grass rats. Grass rats showed superior long-term retention of the MWM, when the training and testing occurred during the day as compared to the night, at a time when nocturnal laboratory rats show superior retention; acquisition of the MWM was not affected by time of day. BDNF/TrkB expression was rhythmic in the hippocampus of grass rats, and the phase of the rhythms was reversed compared to that of nocturnal rodents. Our findings provide correlational evidence for the claim that the circadian regulation of cognition may involve rhythms of BDNF/TrkB expression in the hippocampus and that their phase may contribute to species differences in the optimal phase for learning.

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## 1. Introduction

In mammals, circadian rhythms depend upon the integrity of a master circadian oscillator residing within the hypothalamic suprachiasmatic nucleus (Stephan and Zucker, 1972).

Within neurons of the SCN circadian rhythmic functions are generated by molecular oscillations described as an autoregulatory transcriptional and translational feedback loop; the genes responsible for this feedback loop are labeled clock genes (Ko and Takahashi, 2006). There is evidence of

Abbreviations: BDNF, brain derived neurotrophic factor; TrkB, tyrosine kinase B; ANOVA, analysis of variance; LD, light/dark; LSD, least significant difference; PER, period; SCN, suprachiasmatic nucleus; ZT, Zeitgeber time; DG, dentate gyrus; CA1, cornus Ammon 1; ICC, immunocytochemical; MWM, Morris water maze; MAPK, mitogen activated protein kinase

\*Corresponding author. Fax: +1 517 432 2744.

E-mail addresses: [nunez@msu.edu](mailto:nunez@msu.edu) (C.A. Martin-Fairey), [Martinf3@msu.edu](mailto:Martinf3@msu.edu) (A.A. Nunez).

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local rhythmic expression of clock genes in areas of the brain outside of the SCN, (Abe et al., 2002) including the hippocampus (Duncan et al., 2013; Gilhooley et al., 2011; Ikeno et al., 2013; Lamont et al., 2005; Li et al., 2013; Otolara et al., 2013; Ramanathan et al., 2010b; Wang et al., 2009). These observations bring up the question of the role of hippocampal clock-gene expression in the regulation of hippocampal-dependent cognitive functions.

The phases of clock-gene rhythms of extra-SCN oscillators, such as the one in the hippocampus, are 180° out of phase when diurnal grass rats (*Arvicanthis niloticus*) are compared to nocturnal rodents. Specifically, Ramanathan et al. (2008a, 2008b, 2010a, 2010b) reported that Period (PER) 2 expression peaks during the late light phase in diurnal grass rats and in the late night in nocturnal species (Amir et al., 2006; Amir and Robinson, 2006; Lamont et al., 2005). A similar pattern emerges when other diurnal species, including humans, are compared to nocturnal species (Li et al., 2013; Otolara et al., 2013). Thus, species differences related to the circadian control of hippocampal functions may be determined by the phase of this extra-SCN oscillator.

Possibly related to the phase of extra-SCN oscillators, there is evidence from both animal and human studies that time of training and/or testing can affect learning, retention and performance (Folkard et al., 1985; Folkard, 1990; Gerstner et al., 2009; Smarr et al., 2014). While there is no consensus about the optimal phase for performance across learning tasks, the trend is that both nocturnal and diurnal species perform best when trained and tested during their active phase, and the poorest performance is observed when tested or trained during the inactive phase. In rats, the data support a positive nocturnal bias for the acquisition and retention of a signal-detection task and for retention of the MWM (Gritton et al., 2012), even when time of day differences in acquisition of the MWM task are absent (Valentinuzzi et al., 2004). With some exceptions (see Smarr et al., 2014 for a recent review), hippocampal dependent tasks in both rodent and human studies feature optimal performance when individuals are tested during the active phase of the species (Folkard and Monk, 1985; Furnham and Rawles, 1988; Gritton et al., 2012; Hoffmann, 1992; Payne, 1989; Testu, 1986; Valentinuzzi et al., 2004).

In the hippocampus, several gene products contribute to neural plasticity and the process of learning and retention (Minichiello, 2009; Bekinschtein et al., 2013, 2014; Callaghan and Kelly, 2013; Berchtold et al., 1999; Bova et al., 1998; Cirelli and Tononi, 2000a, 2000b; Dolci et al., 2003; Eckel-Mahan et al., 2008; Hamatake et al., 2011; Ikeno et al., 2013; Katoh-Semba et al., 2008; Roth and Sweatt, 2008; Selcher et al., 1999). Prominent among such plasticity gene products are brain derived neurotrophic factor (BDNF) and its high affinity tyrosine kinase receptor (TrkB). Thus, once the TrkB receptor is occupied by BDNF, a number of signaling cascades, including phosphatidylinositol 3-kinase (PI3-K), mitogen-activated protein kinase (MAPK) and phospholipase C<sub>y</sub> (PLC<sub>y</sub>) are activated (see Tapia-Arancibia et al., 2004 for review). Activation of these signaling cascades has been shown to be involved in many processes important for learning and neural plasticity, including long-term potentiation (Hall et al., 2000; Tyler et al., 2002; Yamada and Nabeshima, 2003). BDNF/TrkB expression

in the hippocampus is important for hippocampal dependent learning and memory (Bekinschtein et al., 2013, 2014; Callaghan and Kelly, 2013; Minichiello et al., 1999; Minichiello, 2009; Yamada and Nabeshima, 2003). Reduction or elimination of BDNF/TrkB expression in the hippocampus results in deficits in both acquisition and retention of hippocampal dependent tasks (Gorski et al., 2003; Korte et al., 1995; Pang and Lu, 2004; Tyler et al., 2002). Studies using late-onset forebrain-specific BDNF knockout mice serve to show the importance of BDNF production in adulthood for normal spatial learning abilities (Vigers et al., 2012). Additionally when the expression of BDNF/TrkB is restored via exercise or pharmacological means, hippocampal dependent memory is rescued (Erickson et al., 2013; Minichiello et al., 1999; Patterson et al., 1996).

Although some discrepancies exist with respect to rhythms of BDNF/TrkB mRNAs in the hippocampus of nocturnal species (Berchtold et al., 1999; Bova et al., 1998; Cirelli and Tononi, 2000a; Ikeno et al., 2013; Schaaf et al., 2000, 2000; Dolci et al., 2003; Golini et al., 2012; Liang et al., 1998), measures of protein abundance show peak hippocampal expression of BDNF/TrkB during the dark phase in adult nocturnal rats (Dolci et al., 2003; Hamatake et al., 2011; Katoh-Semba et al., 2008). Rhythmic expression of BDNF and TrkB may mediate the circadian modulation of hippocampal-dependent memory, and differences in the phase of those rhythms could correlate with differences in the optimal times for learning and/or retention when diurnal and nocturnal species are compared. However, the evaluation of the second part of that claim is hampered by the fact that nothing is known about the features of BDNF/TrkB rhythmic expression in the hippocampus of diurnal mammals.

Here we use the diurnal grass rats to determine if their phase reversal in the rhythmic expression of PER1 and 2 in the hippocampus, when compared with nocturnal rodents, predicts similar phase reversals in the acquisition and retention of a hippocampal-dependent task and in the pattern of expression of BDNF/TrkB in the hippocampus. First, we used the reference memory version of the MWM to determine if time of training affects performance and retention of a spatial navigation task in this diurnal species. Second, we determined expression patterns of BDNF and TrkB protein in the hippocampus of these animals. Since there is evidence of functional heterogeneity and possible differential rhythmic expression of both plasticity and clock genes across the hippocampal formation (Berchtold et al., 1999; Bova et al., 1998; Cirelli and Tononi, 2000a; Ikeno et al., 2013; Schaaf et al., 2000), we evaluated the patterns of protein expression in three distinct regions of the hippocampus, the CA1 area, the dorsal blade of the DG and the hilus.

## 2. Results

### 2.1. Experiment 1

#### 2.1.1. Learning curve

Fig. 1 shows the proportion of animals that reached the platform on the first trial of each day of training (Panel A) and for the average of the four trials for each day of training (Panel B). For both the AM and PM groups, Cochran's Q analyses detected a significant effect of days of training, for

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