

SYSTEMIC ADMINISTRATION OF TWO DIFFERENT ANXIOLYTIC DRUGS DECREASES LOCAL FIELD POTENTIAL THETA FREQUENCY IN THE MEDIAL ENTORRHINAL CORTEX WITHOUT AFFECTING GRID CELL FIRING FIELDS

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Abstract—Neurons coding spatial location (grid cells) are found in medial entorhinal cortex (MEC) and demonstrate increasing size of firing fields and spacing between fields (grid scale) along the dorsoventral axis. This change in grid scale correlates with differences in theta frequency, a 6–10 Hz rhythm in the local field potential (LFP) and rhythmic firing of cells. A relationship between theta frequency and grid scale can be found when examining grid cells recorded in different locations along the dorsoventral axis of MEC. When describing the relationship between theta frequency and grid scale, it is important to account for the strong positive correlation between theta frequency and running speed. Plotting LFP theta frequency across running speeds dissociates two components of this relationship: slope and intercept of the linear fit. Change in theta frequency through a change in the slope component has been modeled and shown experimentally to affect grid scale, but the prediction that change in the intercept component would not affect grid scale has not been tested experimentally. This prediction about the relationship of intercept to grid scale is the primary hypothesis tested in the experiments presented here. All known anxiolytic drugs decrease hippocampal theta frequency despite their differing mechanisms of action. Specifically, anxiolytics decrease the intercept of the theta frequency–running speed relationship in the hippocampus. Here we demonstrate that anxiolytics decrease the intercept of the theta frequency–running speed

relationship in the MEC, similar to hippocampus, and the decrease in frequency through this change in intercept does not affect grid scale. © 2017 IBRO. Published by Elsevier Ltd. All rights reserved.

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INTRODUCTION

Grid cells are strikingly spatially modulated cells that fire action potentials in multiple but very specific locations in an environment as an animal forages for food (Fyhn et al., 2004; Hafting et al., 2005). These firing fields, or grid fields, fire in a pattern corresponding to the corners of tightly packed equilateral triangles tessellating the area traveled. These cells have been primarily recorded in the rodent medial entorhinal cortex (MEC) (Fyhn et al., 2004; Hafting et al., 2005), along with the connected regions of the pre- and parasubiculum (Boccaro et al., 2010). Within these and other regions, “head direction” (HD) cells have also been reported, which fire action potentials when an animal is facing a certain direction (Taube et al., 1990; Sargolini et al., 2006). Together, these cells, along with other activity in these regions, likely contribute to an animal’s sense of spatial location.

Throughout the MEC and connected regions, a prominent 6–10 Hz rhythm (“theta”) appears in the local field potential (LFP) and in the rhythmic firing of single units, such as grid cells. This oscillation was first described in hippocampal LFP and single units (Green and Arduini, 1954; Vanderwolf, 1969; Bland, 1986) and subsequently reported in the MEC in both the LFP and the single unit rhythmicity as well (Mitchell and Ranck, 1980; Alonso and García-Austt, 1987). Grid cells often fire coincidentally with phases of the LFP theta rhythm when an animal traverses through individual firing fields of a grid cell. Coincidental firing can occur either consistently at the same phase of the oscillation (“phase locked”) or at progressively earlier phases across successive theta cycles (“phase precessing”) across each pass through the grid field area (Hafting et al., 2008; Climer et al., 2013). The maintenance of this relationship requires the adaptation of activity to running speed, in order to account for differences in the time it takes to traverse an otherwise

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Abbreviations: 5-HT, 5-hydroxytryptamine (serotonin); LFP, local field potential; MEC, medial entorhinal cortex; OIM, oscillatory interference model.

identical path with differences in speed. In line with this, the frequency of the theta oscillation in the LFP shows a very strong positive correlation with running speed in the MEC (Jeewajee et al., 2008a) and is correlated with grid cell properties in many other ways as well.

Grid fields increase in size and spacing (grid scale) in grid cells recorded along the dorsal to ventral axis of the MEC (Hafting et al., 2005; Sargolini et al., 2006; Brun et al., 2008), which has been linked to changes in theta frequency. This grid scale increase along the axis correlates with the period of the subthreshold membrane potential oscillation recorded in layer II MEC stellate cells *in vitro* (Giocomo et al., 2007). Furthermore, the frequency of the rhythmicity of grid cell firing is inversely correlated with increasing grid field sizes (Jeewajee et al., 2008a; Stensola et al., 2012). Grid scale also increases in response to a novel environment, while the rhythmicity of firing decreases in frequency (the oscillation period increases) (Barry et al., 2012). Consistent with the many correlations reported between grid cells and theta rhythm, theta rhythm has been utilized in many computational models of the location-related activity of grid cells.

Oscillatory interference models (OIMs) take advantage of the prominent theta rhythm to generate the spatially periodic firing of grid cells. The general principle behind these models is that two slightly different oscillations, for example found in the LFP and in a given cell's subthreshold membrane potential oscillations, produce constructive and destructive interference when the peaks of their oscillations align or cancel out, respectively. During times of peak alignment, this drives the given neuron to spike, producing a grid-like pattern. These models use differing oscillation frequencies to produce the different scales of grid cell firing found along the dorsoventral axis and actually predicted that the frequency of intrinsic subthreshold membrane potential oscillations decreases in cells along this axis (O'Keefe and Burgess, 2005; Giocomo et al., 2007). Importantly, the frequency of theta oscillations must increase with running speed in order to maintain consistent firing patterns regardless of velocity, matching biological data (Jeewajee et al., 2008a).

When describing theta frequency in terms of how it relates to grid scale, it is important to consider that theta frequency is very strongly correlated with running speed. Thus, taking the additional variable of running speed into account results in a more accurate and thorough depiction of how theta frequency and grid scale relate. Specifically, the relationship between theta frequency and running speed can be broken down into two dissociable components. Fitting a regression line to the values of theta frequency plotted across increasing running speeds gives both an intercept and a slope value to represent this relationship. Based on the OIM, Burgess (2008) suggested that grid field scale was not directly affected by a change in overall theta frequency, but specifically only by a change in the slope, and not the intercept, of this linear fit (Burgess, 2008). This prediction is partially supported by the findings that exposure to a novel environment increases grid scale and decreases the slope of hippocampal theta frequency plotted across

running speeds (Barry et al., 2012; Wells et al., 2013). However, the prediction that a change in the intercept component of this relationship would be unable to produce similar changes in grid scale compared to those caused by a change in the slope has not been explicitly tested. This prediction about the relationship between grid scale and the intercept of the plot of theta frequency versus running speed is the hypothesis that is tested in the experiments presented here.

One hallmark of all presently known anxiolytic drugs is that they cause a robust decrease in the hippocampal theta frequency elicited via reticular formation stimulation (Coop and McNaughton, 1991; McNaughton and Coop, 1991; McNaughton et al., 2007) or during running in awake behaving animals (Wells et al., 2013). Specifically, Wells et al. (2013) demonstrated that this decrease in hippocampal theta frequency during running comes from a reduction in the intercept and not the slope component of the linear fit between theta frequency and running speed.

The study presented here examined whether systemic administration of a serotonergic anxiolytic or benzodiazepine anxiolytic reduced the intercept component of the relationship between theta frequency and running speed recorded in the MEC, similar to what was reported for these drug types in the hippocampus (Wells et al., 2013). We then tested the prediction that a change in theta frequency acting on the intercept component of the theta frequency-running speed relationship would not produce changes in grid scale, in contrast to data showing changes in grid scale associated with a change in the slope of this relationship.

EXPERIMENTAL PROCEDURES

Subjects

Male Long-Evans rats (Charles River Laboratories) weighing between 350 and 450 g at surgery were used for these studies ($n = 10$). All experimental procedures were approved by the Institutional Animal Care and Use Committee for the Charles River Campus at Boston University. Rats were housed individually in plexiglass cages, maintained on a 12-h light/12-h dark cycle (testing always occurred during the light cycle) and were maintained at ~85% of their ad libitum weight. Prior to surgery, rats were habituated to the experimenter and testing room. The animals were trained to forage in an open field environment (1 m by 1.5 m) for pieces of Froot Loops (Kellogg's). One wall of the otherwise black painted environment was white to provide stable landmark information; cues surrounding the environment were present to provide distal information as well.

Implant

Rats were implanted with recording drives housing up to 16 individually moveable tetrodes (four 12.7 μ m nichrome wires spun together) and 4 reference tetrodes, aimed at the MEC. Tetrodes were gold plated to bring down the impedance to <150 kOhm. The exit of the drive was angled at ~25 degrees in the posterior

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