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The Neural Circuitry Supporting Successful Spatial Navigation despite Variable Movement Speeds

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Highlights:

- Spatial memories remains stable despite dramatic changes in running speed
- Neuronal firing rates and temporal dynamics are both altered by running speed
- Speed-dependent neural codes may help stabilize spatial memories
- Speed codes altered by stimulation of medial septum and brainstem locomotor regions
- Critical to identify which region provides the earliest prediction of speed change

ABSTRACT

Ants who have successfully navigated the long distance between their foraging spot and their nest dozens of times will drastically overshoot their destination if the size of their legs is doubled by the addition of stilts. This observation reflects a navigational strategy called path integration, a strategy also utilized by mammals. Path integration necessitates that animals keep track of their movement speed and use it to precisely and instantly modify where they think they are and where they want to go. Here we review the neural circuitry that has evolved to integrate speed and space. We start with the rate and temporal codes for speed in the hippocampus and work backwards towards the motor and sensory systems. We highlight the need for experiments designed to differentiate the respective contributions of motor efference copy versus sensory inputs. In particular, we discuss the importance of high-resolution tracking of the latency of speed-encoding as a precise way to disentangle the sensory versus motor computations that enable successful spatial navigation at very different speeds.

Keywords
Running Speed; Spatial Navigation; Learning & Memory; Brain Rhythms; Neural Coding; Temporal Code; Rate Code; Hippocampus; Entorhinal Cortex; Secondary Motor Cortex; Medial Septum; Mesencephalic Locomotor Region

MAIN TEXT

Reliable and adaptable navigational capabilities are essential for nearly all animal species. Animals often must take complicated paths through their environments and move at a wide range of speeds. Despite this, most species are remarkably successful at navigating complex environments while simultaneously perceiving sensory stimuli that might alert them to rewards or predators. Contemplating how animals might possess these impressive abilities, Darwin suggested a strategy he termed "dead reckoning". The theory proposed that by combining internal and external motion cues to continuously estimate speed and direction, animals could adequately track their current position relative to a starting point (Darwin 1873; Barlow 1964). Dead reckoning is now commonly referred to as path integration and has taken on a somewhat more restricted definition, focused primarily on the use of internally generated (idiothetic) neural signals (Whishaw et al., 2001; Whishaw and Wallace, 2003; Etienne and Jeffery, 2004; Buzsáki 2005; McNaughton et al., 2006; Buzsáki and Moser, 2013; Chrastil 2013; Geva-Sagiv et al., 2015; Igarashi 2016; Grieves and Jeffery, 2017; Moser et al., 2017). Mammals were first confirmed to utilize path integration in navigation nearly forty years ago (Mittelstaedt and Mittelstaedt, 1980) and multiple brain regions have since been implicated in this function (McNaughton et al., 1996; 2006; Whishaw et al., 1997; 2001; Whishaw and Wallace, 2003; Etienne and Jeffery, 2004; Parron and Save, 2004; Nitz 2006; Wolbers et al., 2007; Moser et al., 2008; 2017; Whitlock et al., 2012; Wilber et al., 2017).

How do neurons computationally represent direction and speed, the variables demanded by path integration theories? For the former, in rodents, Taube and colleagues have found assemblies of neurons deemed head direction cells residing in many navigationally important regions. These neurons integrate vestibular, proprioceptive and other meaningful input to fire only when the animal's head points in a preferred orientation (Taube et al., 1990a; b; Stackman et al., 2002; Peyrache et al., 2015). A number of reviews cover head direction and angular velocity in exquisite detail (Sharp et al., 2001; Taube 2007; Yoder and Taube, 2014; Grieves and Jeffery, 2017; Moser et al., 2017; Campbell and Giocomo, 2018), and here we will instead focus on the neural representation and control of the latter variable, linear running speed. Neural activity patterns associated with locomotion have been studied in a variety of mammals and brain regions for decades (e.g., Green and Arduini, 1954), yielding a multitude of observations that can sometimes be difficult to reconcile. The present review attempts to synthesize these wide-ranging findings with the goal of providing a clearer understanding of the mechanisms, both established and hypothesized, underlying mammalian speed encoding.

Running speed plays a central role in broader theories of spatial cognition. The known circuitry of the brain's so-called 'cognitive map' is formed most prominently by two cell types: hippocampal place cells and entorhinal grid cells. Place cells are pyramidal cells in areas CA1 and CA3 of the hippocampus that selectively fire in one (or sometimes two) locations within a given environment (O'Keefe and Dostrovsky, 1971; Wilson and McNaughton, 1993; Moser et al., 2008; Grieves and Jeffery, 2017). Grid cells (stellate

and pyramidal cells in medial entorhinal cortex as well as principal neurons in pre- and parasubiculum) fire in a similar but repeating manner such that their firing fields produce a tessellating geometric grid over a given environment (Fyhn et al., 2004; Hafting et al., 2005; Sargolini et al., 2006; Moser et al., 2008; Boccara et al., 2010; Grieves and Jeffery, 2017). For spatially invariant representations to be continuously updated in a manner consistent with the subject's movement, the place cell-grid cell network must have access to speed information among other self-motion metrics (Moser et al., 2008; 2017; McNaughton et al., 2006). We begin the present review with a discussion of how speed information appears to be encoded in these two structures before shifting to an examination of the upstream circuitry and computations that may provide this network with speed-modulated inputs.

The Rate Code for Speed in the Hippocampus & Entorhinal Cortex

Neurons utilize two fundamental coding strategies. The first is a "rate code", where one or more neurons increase or decrease their rate of firing in response to a stimulus. The second is a "temporal code", where the precise timing of spikes with respect to either the stimulus or the activity of other neurons carries valuable information (Mehta et al., 2002; Ahmed and Mehta, 2009; Kumar et al., 2010; Ainsworth et al., 2012). It is thus instructive to examine putative hippocampal speed signaling in the contexts of both codes. As a rodent moves faster through the place field of a CA1 neuron the location of the place field remains largely unaltered, but the firing rate of the neuron increases. There is a rich literature documenting this speed-dependent rate increase in CA1 place

cell firing (McNaughton et al., 1983; Wiener et al., 1989; Rivas, et al. 1996; Shen et al., 1997; Zhang et al., 1998; Czurkó et al., 1999; Hirase et al., 1999; Ekstrom et al., 2001; Geisler et al., 2007; Góis and Tort, 2018). Increases in firing rate as a function of speed are also seen in multiple classes of hippocampal inhibitory interneurons, including fast-spiking (FS) and somatostatin-positive (SST+) cells (McNaughton et al., 1983; Ahmed and Mehta, 2012; Czurkó et al., 1999; Nitz and McNaughton, 1999, 2004; Arriaga and Han, 2017). A subpopulation of these cells seem to have particularly (i.e., millisecond scale) temporally-precise speed-rate correlations and respond somewhat poorly to other spatial variables, suggesting that some inhibitory cells may encode speed better than they encode other variables (Kropff et al., 2015; Góis and Tort, 2018; and see MEC section below). The fact that inhibitory cells are usually the ones found to best encode speed has a lot to do with the fact that they tend to fire at almost all locations within a given environment, unlike place cells (excitatory pyramidal neurons) that fire in restricted regions of space. Thus, inhibitory neurons are more likely to sample the full range of speeds over which an animal runs. However, by simply taking the population spiking rate of all recorded (excitatory) place cells, the speed-place cell firing rate correlation in CA1 can be clearly seen (McNaughton et al., 1983; Geisler et al., 2007; Guger et al., 2011; Ahmed & Mehta, 2012; Maurer et al., 2012). Thus, the speed rate code is built into the firing properties of both inhibitory and excitatory hippocampal neurons. Subgroups of both CA1 place cells and inhibitory interneurons have also displayed negative correlations between firing rate and speed (Wiener et al., 1989; Yu et al., 2017, Arriaga and Han, 2017). However, it is unclear whether these cells are indeed preferentially encoding low movement speeds or instead are influenced by

selective firing during immobility-associated hippocampal sharp-wave ripple events when the animal is relatively still (Buzsáki 2015; Colgin 2016).

Rate encoding of speed systematically varies along the septotemporal ('long') axis of the hippocampus, with the impact of speed on CA1 firing rates diminishing as one moves from the septal to the temporal pole of the hippocampus (Maurer et al., 2005). A parallel anatomically-dependent change also exists for place field size, which increases from the septal to the temporal hippocampal pole (Maurer et al., 2005; Jung et al., 1994; Kjelstrup et al., 2008; Ahmed and Mehta, 2009). These findings again point to a tight computational link between speed and spatial encoding in the hippocampus.

As the other half of the canonical 'cognitive map' circuit, the MEC is heavily interconnected with the hippocampus and may help to shape the firing patterns of place cells, although the precise impact of this functional connectivity is still an active area of investigation (Quirk et al., 1992; Moser et al., 2008; Ahmed and Mehta, 2009; Buzsáki and Moser, 2013; and see Sasaki et al., 2015 for an excellent review of MEC circuits and their impact on hippocampal activity). Most cell types present in the MEC population, including excitatory grid cells, excitatory head-direction cells, and inhibitory interneurons, exhibit speed-modulated firing rates similar to their hippocampal counterparts (Sargolini et al., 2006; Wills et al., 2012; Buetfering et al. 2014; Hinman et al., 2016; Reifenstein et al., 2016; Gil et al., 2018). However, recent work has shown that the rate-speed relationships of most functionally-dedicated cell types can be complex and heterogeneous, including 'saturating' speed modulations that plateau at

intermediate running speeds or, similar to findings in the hippocampus, monotonically negative speed-rate relationships (Hinman et al., 2016; Hardcastle et al., 2017; Heys and Dombeck, 2018; Mallory et al., 2018). Partial evidence for a dedicated 'speed cell' population in MEC (in addition to the hippocampal population discussed above) has also recently emerged: these cells exhibit "context-invariant" firing that either increases or decreases with running speed (Kropff et al., 2015; Tanke et al., unpublished). However, the existence of MEC cells that encode nothing but speed is clearly not the norm. Typically, when single units in MEC show speed-related encoding, they do so in conjunction with other spatial metrics (Sargolini et al., 2006; Perez-Escobar et al., 2016; Hardcastle et al., 2017; Góis and Tort, 2018; Ye et al., 2018), so it may be more likely that a 'speed cell' population simply weights speed in its output slightly more strongly than other spatially-relevant variables. The precise encoding properties of these cells thus demands further investigation, both in terms of function and in terms of the inputs that shape them. Recent work further suggests that nearly half of the putative speed cells may be inhibitory (Perez-Escobar et al., 2016; Ye et al., 2018), allowing them to shape grid cell output in a partially speed-dependent manner (Miao et al., 2017). This, too, should not come as a surprise because, as discussed above, inhibitory neurons in the hippocampus have long been known to strongly encode speed (in addition to other spatial parameters) in large parts of the environment (Czurkó et al., 1999; Nitz & McNaughton, 1999; 2004; Góis and Tort, 2018)

Another major source of input to CA1 is hippocampal area CA3, which itself receives spatially modulated input from MEC (for review of this functional anatomy, see

McNaughton et al., 2006; Ahmed and Mehta, 2009; Knierim 2015; Igarashi 2016; Grieves and Jeffery, 2017). While the CA3 population has been reported to also show rate increases with running speed (McNaughton et al., 1983), the correlation between the two seems to be weaker than in CA1 (Kay et al., 2016). Much work has further suggested that the relative strength of CA3 input to CA1 is substantially reduced during running behavior compared to epochs of immobility (Segal 1978; Winson and Abzug 1978; Kemere et al., 2013). In agreement with these findings, a recent study found that speed increases drive MEC and CA1 rate changes much more similarly to each other than to CA3 cells, which display a weaker speed dependence (Zheng et al., 2015). Furthermore, division of the MEC layer II population into CA3- or dentate gyrus (DG)-projecting stellate cells (also called 'ocean cells') and CA1-projecting pyramidal cells (also called 'island cells') reveals a much higher proportion of speed-modulated island cells than ocean cells and stronger speed modulation of island activity (Sun et al., 2015). It should be noted, however, that certain DG populations have also been reported to exhibit positive speed-rate relationships (McNaughton et al., 1983; Nitz and McNaughton, 1999), and that the comparative nature of these relationships with those elsewhere in the hippocampal-entorhinal complex remain undefined to our best knowledge.

Hippocampal area CA2, which has recently been suggested to innervate CA1 and influence its output (Kohara et al., 2014), may also participate in speed encoding. Recent examination of this area's spatially relevant output revealed two populations of cells with speed-rate relationships, one with a positive influence and one with a negative

influence (Kay et al., 2016). These results reflect similar findings from the same group in CA1 (Yu et al., 2017).

Thus, running speed clearly and robustly alters the rate code in the circuitry most heavily implicated in spatial navigation.

The Temporal Code for Speed in the Hippocampus & Entorhinal Cortex

Theta Rhythms & Running Speed

Two hippocampal oscillations exhibit prominent speed-based modulation: theta (roughly 6-12Hz) and gamma (roughly 25-100Hz). Theta oscillations are canonically associated with active behavioral states such as locomotion or REM sleep (Buzsáki 2002; 2005; Colgin 2013; Korotkova et al., 2018). The relationship between theta and running speed has been an active research topic for nearly half a century, beginning with Vanderwolf's seminal finding that the locomotion speed of a rat roughly correlated with the strength of the hippocampal EEG theta signal (Vanderwolf 1969). This relationship was further outlined in the following years by studies specifically detailing enhancements of theta amplitude and frequency at high running speeds (Whishaw and Vanderwolf, 1973; McFarland et al., 1974; Arnolds et al., 1979). Various contemporary studies have replicated both effects in mice and rats throughout the hippocampus (Shen et al., 1997; Rivas et al., 1996; Sławińska and Kasicki, 1998; Geisler et al., 2007; 2010; Bender et al., 2015; Gereke et al., 2017; Scaplen et al., 2017; Mikulovic et al., 2018, Winne et al., 2019). A recent study using intracranial electrodes implanted in patients with epilepsy

showed that medial temporal theta power, while much weaker in humans than in rodents, does increase somewhat during periods of faster physical movement (Aghajan et al., 2017). However, the precise strength of the relationship between movement speed and hippocampal theta power and frequency in humans remains to be determined. In addition to changes in theta power and frequency, the waveform shape of theta oscillations also appears to shift at higher running speeds in rodents from a classic sinusoidal pattern to a sawtooth-like pattern (Buzsáki et al., 1983; Terrazas et al., 2005; Sheremet et al., 2016).

The correlation between hippocampal theta and running speed is most prominent in CA1: when speed modulation of theta was tracked in rats in CA1, CA3, and DG, frequency changes occurred in all three regions but strong power changes were limited to CA1 (Montgomery et al., 2009; Hinman et al. 2011). Given that CA1 receives anatomically distinct inputs from those of CA3 and DG (Amaral and Witter, 1989; Witter and Amaral, 2004), it seems likely that the observed findings reflect differential delivery routes for the putative speed signal to each hippocampal area. Long axis effects on the CA1 temporal signal also seem to exist, with speed modulations of theta power and waveform shape appearing strongest in dorsal CA1 and diminishing in ventral CA1 (Maurer et al., 2005; Hinman et al., 2011; Patel et al., 2012; Hinman et al., 2013; Sheremet et al., 2016). Modulations of frequency remain constant along the long-axis of CA1, however (Maurer et al., 2005; Hinman et al., 2011; but see Sheremet et al., 2016), a division that might reflect the differential projections along the long axis and their proposed resultant functional gradients (Strange et al., 2014).

MEC exhibits similar theta oscillatory activity during locomotion to that observed in the hippocampus, and, reflecting communication between the two regions, theta-band coherence with the hippocampus (Buzsáki et al., 1986; Brankačk et al., 1993). Theta power and frequency in the MEC also both scale with running speed (Hinman et al., 2016; Jeewajee et al., 2008; Wills et al., 2012), and thus, entorhinal-hippocampal theta-band coherence improves as a function of speed (Hinman et al., 2011). However, MEC fails to display a CA1-like long axis effect on the speed-theta relationship, and as such there subsequently exists a septotemporal drop-off in the speed-based inter-area theta coherence (Hinman et al., 2011).

While most of the literature covering the entorhinal speed signal describes modulations occurring specifically in MEC, it should be noted that speed effects on theta frequency and power have also been reported in the lateral entorhinal cortex (LEC) (Hinman et al., 2011), despite being a markedly less spatially modulated region (Hargreaves et al., 2005). This phenomenon may need further investigation, however, as it contradicts both previous and subsequent work demonstrating a paucity of either LFP theta or theta-rhythmic spiking by cells in this region (Deshmukh et al., 2010; Shay et al., 2012). LEC sends its own projections throughout the hippocampus (Witter and Amaral, 2004; Agster and Burwell, 2013), and recent work has accordingly demonstrated that inactivating the LEC with muscimol, a GABAergic agonist, results in a decrease in hippocampal CA1 theta power and frequency, and reduces the strength of hippocampal speed-theta correlations (Scaplen et al., 2017). Both the LEC and MEC have recently been

implicated in temporal encoding (Heys and Dombeck, 2018; Tsao et al., 2018), a role that one would certainly expect to influence any downstream encoding of a variable defined with respect to time (e.g., speed). Thus, speed modulated inputs from both the MEC and LEC play a role in shaping speed and theta-dependent computations in the hippocampus itself.

Gamma Rhythms & Running Speed

Gamma oscillations, often coupled to the theta rhythm, are common signatures of processing throughout the hippocampus (Buzsáki et al., 1983; Bragin et al., 1995; Csicsvari et al., 2003; for review, see Colgin and Moser, 2010) and neocortex (Gray et al., 1989; Sanes and Donoghue, 1993; Fries et al., 2001; Sirota et al., 2008). Neocortical gamma rhythms play important roles in sensory perception, decision-making, and attention and have been proposed to 'bind' distributed networks encoding related information (Singer 1999; Engel and Singer, 2001; Engel et al., 2001; Fries 2005; 2009; but see Ray and Maunsell, 2010). Given the speed-dependent rate modulation of inhibitory FS neurons discussed above and the critical role FS cells play in generating gamma oscillations (Cardin et al., 2009; Börgers et al., 2005; Traub et al., 1999; Ahmed and Cash, 2013), one would expect hippocampal gamma rhythms to also be speed modulated. Indeed, numerous studies have now documented precise changes in hippocampal gamma at different running speeds. Hippocampal CA1 gamma frequency in rats (Ahmed and Mehta 2012; Kemere et al., 2013) and gamma power in mice (Chen et al., 2011; Gereke et al., 2017; Lopes-dos-Santos et al., 2018) have both

been shown to increase with faster running speeds. Similar changes in CA1 gamma have been noted as a function of increasing acceleration (Kemere et al., 2013).

Recent evidence has shown that speed exerts a larger influence on 'fast' gamma frequencies (~60-100 Hz) compared to that on 'slow' gamma (~25-55 Hz) (Zheng et al., 2015; Trimper et al., 2017; and see Gereke et al., 2017 for experience-dependent changes in the speed-gamma relationship). Moreover, decreases in CA1 slow gamma power with increased speed have also been reported (Ahmed & Mehta, 2012; Kemere et al., 2013; Lopes-dos-Santos et al., 2018). Given that fast and slow CA1 gamma are differentially coupled to MEC and CA3 inputs, respectively (Colgin et al., 2009), these findings in conjunction with the aforementioned findings for differential rate-speed relationships throughout this network suggest that MEC grid cells are likely to exert stronger influences over CA1 place cells at faster running speeds, especially when compared to influence from CA3. This idea is further supported by the finding that transgenic mice lacking CA3 innervation of CA1 display unaffected speed modulation of CA1 fast gamma (Middleton and McHugh, 2016).

There may be key computational advantages to speeding up rhythms at faster running speeds. As one moves more quickly through an environment, there is a need for faster transitions between spatially modulated place and grid cell assemblies (Dragoi and Buzsáki, 2006; Harris 2005). The changes in the precise frequency of both gamma and theta rhythms may facilitate this process (Geisler et al., 2007; Maurer et al., 2012; Ahmed and Mehta, 2012), helping to maintain a spatially-invariant representation of our

environment even as we move at very different speeds. Despite this tantalizing theoretical framework, additional work is needed to causally establish how precise changes in brain rhythms at different running speeds impact spatial memory formation (Trimper et al., 2017).

How do speed signals get to the hippocampus and entorhinal cortex?

The speed-dependent increases in firing rate of CA1 and CA3 place cells are, at least partially, driven by the aforementioned inputs from MEC cells, which themselves are speed-modulated (Sargolini et al., 2006; Wills et al., 2012; Buetfering et al. 2014; Hinman et al., 2016). But what causes MEC cells to increase their rates at faster running speeds? Among the regions projecting to the entorhinal-hippocampal complex, the medial septum emerges as the strongest candidate for the critical supplier of this speed signal. The role of this circuit in speed processing has been recently reviewed (Campbell and Giocomo, 2018), but here we expand upon this discussion. The medial septum has heavy reciprocal connections with both the MEC and the hippocampus (Swanson and Cowan, 1979; Alonso and Köhler, 1984), and its role in regulating the hippocampal theta rhythm is extremely well established (Winson 1978; Kramis and Vanderwolf, 1980; Stewart and Vanderwolf, 1987, Bland and Colom, 1993; Bland et al., 2006; for review, see Colgin 2013; 2016; but see Goutagny et al., 2009). Furthermore, pharmacological inactivation of the medial septum has been shown to strongly impact hippocampal-entorhinal temporal and rate speed encoding (Mizumori et al., 1990; Hinman et al., 2016). The exact nature of this influence is unclear, however, as such manipulation has been reported to enhance the downstream speed code while

simultaneously diminishing the temporal code (Hinman et al., 2016), warranting further investigation, ideally using more spatially precise, non-pharmacological manipulations.

Neurons in the medial septum (often combined with the related diagonal band of Broca to form the acronym 'MSDB') generally fire at higher theta-modulated rates at increased running speeds (King et al., 1998; Zhou et al., 1999; Justus et al., 2017). These neurons can be divided into three distinct subpopulations, all of which target the entorhinal-hippocampal complex: glutamatergic, GABAergic, and cholinergic (Fig. 1A) (Sotty et al., 2003; Colom et al., 2005). Glutamatergic cells, the most recently characterized subpopulation (Manns et al., 2001; Sotty et al., 2003; Colom et al., 2005), display linear activity increases with speed (Fig. 1A) (Furhmann et al., 2015, Justus et al., 2017), as do septal glutamatergic axons in the MEC (Justus et al., 2017). These projections have been shown to target various cell types throughout the MEC and hippocampus, including pyramidal cells and inhibitory interneurons (Huh et al., 2010; Sun et al., 2014) and, upon optogenetic-based activation, increase the firing rates of many of these cells (Fuhrmann et al., 2015; Justus et al., 2017). Such results implicate septal projections in mediating or shaping the various rate and temporal codes for speed in the hippocampal-entorhinal complex, an idea further supported by the finding that optogenetic stimulation of these projections at theta frequencies successfully elicits CA1 theta at matching frequencies (Fig. 1A) (Fuhrmann et al., 2015; Robinson et al., 2016). However, the specific mechanisms these projections might utilize to facilitate downstream speed encoding remain unclear, as septal glutamatergic innervation has been suggested to be most effectively integrated by pyramidal cells in MEC (Justus et al., 2017), while

alternatively, initiating a disinhibitory circuit in CA1 (Fuhrmann et al., 2015). Importantly, optogenetic activation of these projections can also induce locomotion at a speed that is correlated to the stimulation frequency (Fig. 1A). Moreover, when local MSDB glutamatergic transmission is pharmacologically blocked during the same optogenetic manipulation, locomotion persists despite the termination of hippocampal signaling effects, indicating that the basal forebrain may somehow discriminate between descending motor commands and efference copy-like metrics (i.e. speed) of those same commands utilized by the spatial representation circuit (Fuhrmann et al., 2015).

GABAergic and cholinergic MSDB cells have been studied extensively for much longer than the glutamatergic population, the former having a well-characterized role in 'pacing' theta in the hippocampal-entorhinal complex (Mitchell et al., 1982; Freund and Antal, 1988; Hangya et al., 2009; Unal et al., 2015). Septal GABAergic projections directly target hippocampal interneurons (Freund and Antal, 1988; Tóth et al., 1997; Sun et al., 2014), while cholinergic cells project to interneurons and pyramidal cells (Cole and Nicoll, 1983; Widmer et al., 2006; Sun et al., 2014). Such features position these cell types well to meaningfully contribute to entorhinal-hippocampal speed encoding, an idea corroborated by both cell types' reported rate increases with speed (King et al., 1998; Davidson et al., unpublished) (Fig. 1A). In agreement with this concept, optogenetic activation of GABAergic cells has been reported to override the effects of locomotion on theta, and, as seen in the glutamatergic population, possibly influence locomotion itself, although the latter conclusion is less clear (Bender et al., 2015) (Fig. 1A). MSDB cholinergic projections modulate hippocampal cellular membrane potentials

and firing rates (Ropert 1985; Haam et al., 2018), and possibly play important roles in

hippocampal theta generation (Smythe et al., 1992; Buzsáki 2002; Haam et al., 2018;

Mikulovic et al., 2018). Blocking MEC muscarinic transmission disrupts the local theta

frequency-speed relationship (Newman et al., 2013). However, investigations directly

and selectively activating the MSDB cholinergic population have yet to elucidate a clear,

causal role in either speed-like signaling in the entorhinal-hippocampal complex or

locomotion (Nagode et al., 2011; Vandecasteele et al., 2014; Carpenter et al., 2017;

Haam et al., 2018) (Fig 1A).

This evidence points towards a role for basal forebrain nuclei in delivering and

controlling the hippocampal-entorhinal speed signal while possibly somehow

simultaneously initiating or relaying a related locomotive command. This idea is further

supported by results from studies manipulating speed signaling in the entorhinal-

hippocampal complex through local pharmacological disruptions of all three kinds of

septal transmission (Bouwman et al., 2005; Hinman et al., 2013; Jacobson et al., 2013;

Newman et al., 2013).

The Mesencephalic Locomotor Region and its role in locomotion and speed-signaling

Where might the MSDB receive information that could be put towards both locomotion

modulation as well as speed signaling for spatial representation maintenance? In

surveying the regions projecting to MSDB, the Mesencephalic Locomotor Region (MLR)

is one candidate area that stands out: Electrical stimulation of this behaviorally-defined

group of brainstem nuclei, typically but not always including the pedunculopontine

tegmental nucleus (PPN) and the cuneiform nucleus (Cun) (Noga et al., 2017), initiates and controls locomotion in most mammals (Shik et al., 1966; Skinner and Garcia-Rill, 1984; Grillner et al., 1997; Ryczko and Dubuc, 2013). While study of this vaguely-defined region has primarily focused on its role in controlling descending motor output (Shik et al., 1966; Mori et al., 1978; Takakusaki 2008), evidence for a possible second role for MLR signaling has emerged: The MLR seems to induce efference copy-like processing changes in higher structures through its ascending projections to the basal forebrain (Pinto et al., 2013; Fu et al., 2014; Lee et al., 2014), suggesting that it may be at least one source of the speed-modulated signals discussed thus far in this review.

Indeed, MLR neuronal activity has been shown to both positively and negatively correlate with running speed (Fig. 1B) (Norton et al., 2011; Lee et al., 2014; Roseberry et al., 2016). Moreover, theta oscillations throughout the MLR have been recently reported to increase with locomotion initiation and scale in power with speed (Noga et al., 2017). Unpublished work has further suggested that this signaling is apparently sufficient for the entrainment of downstream speed encoding in the MSDB (Carvalho et al., unpublished; Tanke et al., unpublished). A notable feature of MLR speed signaling is that, as is the case for encoding throughout the circuit in the MDSB (Fuhrmann et al., 2015), MEC (Kropff et al., 2015), and hippocampus (Wyble et al., 2004; Vanderwolf 1969; Arriaga and Han, 2017), it seems to be 'prospective' by up to several hundred milliseconds, i.e. neuronal activity patterns reflect future speeds and locomotive events more accurately than ongoing events (Lee et al., 2014; Roseberry et al., 2016). Prospective coding is a notable feature of both grid cell and place cell firing fields

(Kropff et al., 2015), and such temporal consistency between changes in locomotive-related speed signaling and updating of the spatial representation system bolsters the arguments for both speed-based updating mechanisms as well as efference copy mechanisms in generating the speed signal. It should be noted, however, that retrospective coding (i.e., speed coding lagging behind an animal's actual ongoing navigation) has also been reported for speed cells in the hippocampus (Kropff et al., 2015; Góis and Tort, 2018). Further exploration of the temporal relationship between speed signaling and behavior is thus warranted.

However, many important characteristics of MLR speed encoding remain unclear. The exact contributions of specific cell types to speed signaling are underreported, especially that of cholinergic cells, despite the ability of all cell types to modify active running speed (Fig. 1B) (Roseberry et al., 2016). Additionally, although it has been suggested that the same cells mediate both the descending locomotive and resultant ascending processing changes (Lee et al., 2014), the complexity and vagueness of MLR anatomy demands rigorous confirmation of this finding, especially when possible confounding effects of activation of arousal nuclei in the PPN, a member of the reticular activating formation (Nauta and Kuypers, 1958), are considered (Vinck et al., 2015; Campbell and Giocomo, 2018). Furthermore, outside of unpublished data (Carvalho et al., unpublished; Tanke et al., unpublished), to our best knowledge a direct link between MLR signaling and hippocampal-entorhinal speed encoding has yet to be established (Fig. 1B).

Ultimate source of the neural speed signal: motor or sensory or both?

The motor circuitry directly upstream of the MLR (Garcia-Rill 1986) seems to contain robust speed coding as well (Fig. 2A). Rate codes for speed have been reported in the motor cortex (Leinweber et al., 2017), striatum (Kim et al., 2014) and substantia nigra pars compacta (Barter et al., 2015), whereas theta and gamma oscillatory temporal codes have been reported in both motor cortex (von Nicolai et al., 2014) and striatum (Masimore et al., 2005; von Nicolai et al., 2014; but see Lalla et al., 2017). Additionally, optogenetic activation of striatal populations encoding speed modulates downstream MLR signaling (Roseberry et al., 2016) as well as locomotion (Bartholomew et al., 2016; Roseberry et al., 2016) (Fig. 1C). Taken together, this evidence suggests that internally-generated motor commands give rise to the speed signals utilized in the hippocampus and MEC for spatial representation maintenance through an efference copy-like mechanism. Corroborating this hypothesis, removing motor and/or proprioceptive cues by passively moving an animal in a cart around an already-run track diminishes speed modulations of grid cell and place cell firing rate as well as MEC and hippocampal theta power and frequency (Terrazas et al., 2005; Lu and Bilkey, 2010; Winter et al., 2015). Moreover, motor cues might also be sufficient to some degree for the maintenance of theoretically speed-dependent internal spatial representations, as animals running on a running wheel (i.e., without a true 'environment' to navigate) have been reported to still show hippocampal place sequences (Pastalkova et al., 2008; Wang et al., 2014).

However, the original premise of dead reckoning maintains two possible sources from which speed information can be derived: externally- or internally-generated cues. While efference copies might represent the latter, the former is most likely represented by sensory systems encoding information such as changes in optic or tactile flow. Logic and intuition thus demand that these types of informational streams should be seriously examined as an alternative origin of hippocampal-entorhinal speed signaling. And indeed, as discussed below, movement speed is directly encoded in the sensory systems.

Optic flow speed seems to be encoded by LGN and primary visual cortical cells (Roth et al., 2016; Saleem et al., 2013; Erisken et al., 2014; but see Niell and Stryker, 2010), while specialized cells exist in rodent barrel cortex that encode the speed at which whiskers drag along the ground (Chorev et al., 2016). A preliminary study has also reported the presence of hippocampal-entorhinal-like "speed-responsive" interneurons in the barrel cortex (Long and Zhang, 2018), inviting further investigation of this possibility. Some degree of sensory functioning seems necessary for speed signal generation as well, as complete darkness has recently been shown to disrupt speed modulation of MEC theta and grid cell activity in addition to other features of the grid cell network (Chen et al., 2016). And while it remains less well-investigated than the motor circuitry discussed in this review, there also seems to be at least one possible circuit with consistently reported speed encoding that might be able to transmit sensory-derived speed information to the hippocampal-entorhinal complex: the visual cortical areas project to posterior parietal cortex (Wilber et al., 2017; Yang et al., 2017; Miller

and Vogt, 1984), which projects to the postrhinal complex (Furtak et al., 2012; Burwell and Amaral, 1998), and onto the hippocampus and MEC (Burwell and Amaral, 1998; Agster and Burwell, 2009) (Fig. 2B).

If both sensory- and motor-derived estimates of speed are indeed required to eventually generate speed signaling in the hippocampal-entorhinal complex, the two informational streams must at some point interact and influence each other to give rise to a unified speed signal. Evidence for a kind of comparison or reconciliation process has already emerged in the early visual system: Studies investigating responses to incongruent visual and running speed have noted either mismatch-based (Keller et al., 2012; Roth et al., 2016) or integrative responses (Saleem et al., 2013; Roth et al., 2016), with implications for the downstream place cell network (Chen et al., 2013; 2019).

Despite these findings, a compelling argument can be made for a somewhat deterministic influence of the motor system over sensory information in speed signal generation. Locomotion influences general and speed-specific sensory cortical processing through an efference-copy-like mechanism (Niell and Stryker, 2010; Ayaz et al., 2013; Erisken et al., 2014; Schneider et al., 2014; Zhou et al., 2014; Dadarlat and Stryker, 2017). The motor cortex and MLR have been implicated in mediating these changes by acting through direct innervation of sensory areas (Schneider et al., 2014; Leinweber et al., 2017) and ascending basal forebrain projections (Pinto et al., 2013; Fu et al., 2014; Lee et al., 2014), respectively. The MLR might in turn be dependent upon the basal ganglia or other higher motor planning regions to mediate these changes

(Roseberry et al., 2016). Moreover, various classes of units throughout the visual system are tuned to running speed and remain so in the absence of visual input (Fu et al., 2014; Pakan et al., 2016; Roth et al., 2016; Erisken et al., 2014; Saleem et al., 2013; Christensen and Pillow, 2017), while M2 axons in V1 have "predictive" activity ramp-ups that precede locomotion initiation, lead similar responses by V1 cells, and also scale with running speed (Leinweber et al., 2017). A similar M2 projection to auditory cortex has been shown to carry an efference copy that precedes locomotion and inhibits local responses to auditory stimuli (Schneider et al., 2014; Fig 2). Lastly, initial reports claim that layer V contains the highest share of speed-tuned neurons in V1, whereas layer IV had the smallest, suggesting that the visually-derived speed signal may derive more strongly from other cortical inputs rather than from raw sensory inputs coming into layer IV from the LGN (Christensen and Pillow, 2017). Together, this evidence strongly suggests that an efference copy of the motor-derived speed signal arrives in sensory cortices through multiple pathways before a sensory-derived speed estimate can be made and influences that sensory-based estimate.

It seems unlikely, however, that the motor system completely dominates the sensory system's speed signal determination; instead, the speed signal that ends up in the hippocampal-entorhinal complex is probably derived from some combination of the two sources. Recent findings have begun to strongly support this more nuanced view. Predictive motor-related signals from M2 can be modified after locomotion onset to reflect visual flow or the expected changes in visual flow based on the visual scene before locomotion onset (Leinweber et al., 2017). Furthermore, the tuning of MEC

speed cells is retained in the dark, yet importantly, with reduced specificity (Kropff et al., 2015; Perez-Escobar et al., 2016). Additionally, these cells can more faithfully reflect either visual or locomotive inputs during bidirectional manipulation of the gain between visual flow and running speed in a virtual reality environment (Campbell et al., 2018); similar effects of gain manipulations on MEC theta frequency may also occur (Chen et al., 2019). Lastly, in a recent experiment examining MEC spatial encoding in the vertical plane, both rate and temporal speed signals were altered, a finding the authors attributed to a likely change in both the incoming sensory input and efference copies (Casali et al., 2019). Further investigation is thus required to fully elucidate the mechanisms by which sensory and motor input combine to create a unified speed signal, while carefully tracking the precise prospective or retrospective coding latency in each relevant brain region.

Vestibular contributions to the speed code

Another sensory modality warranting serious consideration in the search for the speed signal origin is the vestibular system. Vestibular information has been suggested to be integrated with information from other senses such as vision as well as motor information to produce a substantial portion of the sensation of self-motion (Taube 2007; Cullen 2012; Dumont and Taube, 2015; Cullen and Taube, 2017). Accordingly, there is evidence that vestibular input is important for supporting head-direction cell output as well as the spatial navigational functions of the hippocampus and entorhinal cortex (Smith 1997; Smith et al., 2005; 2010; Cullen 2012; Jacob et al., 2014; Shinder and Taube, 2014; Yoder and Taube, 2014; Harvey et al., 2018). Similarly, hippocampal

theta rhythms are influenced by some degree of vestibular input (Russell et al., 2006; Aitken et al., 2018).

There exists a well-delineated circuit carrying vestibular signals to the navigational network: information from the vestibular nuclei is sent to the dorsal tegmental nucleus (via the nucleus prepositus and the supragenual nucleus) to the dorsal tegmental nucleus (Taube 2007). From there, it is sent to the lateral mammillary nucleus and on to the anterior thalamic nuclei, which transmits it onto the subiculum and MEC (Taube 2007; Hitier et al., 2014; Cullen and Taube, 2017). This circuit is largely assumed to primarily encode direction; indeed head-direction cells exist in many of these regions, and lesioning of most constituents abolishes the head-direction signal (Cullen and Taube, 2017). However, it is likely that this vestibular input shapes the linear speed signal as well in the entorhinal-hippocampal system: cells in the dorsal tegmental nucleus, lateral mammillary nucleus and anterior thalamic nucleus all encode linear head velocity (Taube, 1995; Stackman and Taube, 1998; Bassett and Taube, 2001; Yoder et al., 2015). Additionally, inactivation of the vestibular nuclei has been reported to dampen entorhinal speed encoding (Jacob et al., 2014), while lesions of the perirhinal cortex, which likely receives vestibular input from the vestibular nuclei via a different circuit (Hitier et al., 2014), have been demonstrated to disrupt downstream hippocampal speed signaling (Muir and Bilkey, 2003; Lu and Bilkey, 2010).

The vestibular system's contribution to spatial processing can perhaps be best studied using recently developed experimental systems in which the test animal is head-fixed

(usually with a virtual reality environment to navigate), which likely alter vestibular sensation. Using these systems, multiple groups have captured various features of spatial processing, including grid cell and place cell activity, in addition to related speed modulations, with qualitatively similar profiles to signaling found in freely-moving animals in real environments (Harvey et al., 2009; Chen et al., 2013; 2019; Domnisoru et al., 2013; Aronov and Tank, 2014; Heys et al., 2014; Justus et al., 2017; Campbell et al., 2018). Conversely, differences *have* been reported between the spatial tuning of cells in virtual reality relative to real-world navigation (Ravassard et al., 2013; Aghajan et al., 2015; Chen et al., 2018). Thus, the exact degree to which vestibular and other self-motion metrics are disrupted by virtual reality and/or head-fixation remains unclear and is an important issue to address moving forward (for further discussion, see Minderer et al., 2016).

Interestingly, CA1 speed-rate relationships have been reported to be maintained in animals with vestibular lesions (Russell et al., 2006). It has been suggested that the visual system may be able to compensate for missing vestibular contributions to speed signaling in these experimental conditions (Jacob et al., 2014), but this notion may be complicated by findings of altered speed signaling in vertically-locomoting animals who, one would imagine, are also experiencing altered vestibular afferents (Casali et al., 2019). These conflicting results demand further, rigorous study of the self-motion signals utilized by spatial navigational networks. Nevertheless, vestibular information clearly interacts with efference copies from the motor system and information from

various external sensory systems such as vision to generate both angular and linear speed signals for navigational purposes (Dumont and Taube, 2015).

Summary & Future Directions

Here, we have reviewed the evidence for robust rate and temporal codes for speed throughout the mammalian brain. These codes are especially well-documented in the hippocampus and entorhinal cortex, where they likely play essential roles in the maintenance of stable spatial representations. Codes for speed exist in both upstream motor and sensory circuitry, and we argue that the work performed thus far suggests these different modalities interact in a complex way to ultimately give rise to the speed information processed by the hippocampal-entorhinal complex.

A number of unresolved issues preclude a more complete understanding of the neural speed signal. One such issue concerns the purpose of diverse rate codes. For example, in nearly every region reviewed here, positively- and negatively-speed modulated cells have been reported. Further investigation is required to determine whether these opposing codes work cohesively to produce a singular, robust internal measure of speed or if they might instead either conflict with each other or possibly encode distinct components of speed or velocity.

With respect to the origin of the unified speed hippocampal-entorhinal speed signal, both motor and sensory speed coding should be investigated simultaneously to parse out their relative relationships to each other (as in Campbell et al., 2018) and to downstream speed signaling. Speed estimates could be theoretically distilled by many sensory modalities, and yet speed signaling has only begun to be examined in full in the visual system. Why might the auditory system, for instance, receive an efference copy from M2 of an opposite polarity from that received by the visual system (Schneider et al., 2014; Leinweber et al., 2017; Zhou et al., 2014; Dadarlat and Stryker, 2017), and do these distinct polarities impact the relative contribution of either sense to the hippocampal-entorhinal speed signal?

The idea that speed signaling in noncanonically motor control regions such as MSDB (Fuhrmann et al., 2015; Bender et al., 2015; but see Bland et al., 2006) and possibly the hippocampus (Bender et al., 2015) can influence ongoing locomotive behavior also invites further discussion. How might these structures control descending locomotive outputs? A few of the groups reporting these effects (Fuhrmann et al., 2015; Bender et al., 2015) have proposed various circuits that may relay septo-hippocampal/entorhinal speed signaling to locomotive control regions, primarily ones converging upon the ventral tegmental area (VTA) (Fig. 2C). This putative functional anatomy includes a direct MSDB-to-VTA projection (Fuhrmann et al., 2015; Geisler and Wise, 2008) and a hippocampal-originating projection that works through first the lateral septum and next the lateral hypothalamus before reaching the VTA (Bender et al., 2015; Geisler and Wise, 2008). All of these regions have been shown to contain rate codes for speed

(Zhou et al., 1999; Puryear et al., 2010; Wang and Tsien, 2011; Bender et al., 2015) and to modulate locomotion upon stimulation (Kalivas et al., 1981; Parker and Sinnamon, 1983; Christopher and Butter, 1968; Patterson et al., 2015; Bender et al., 2015). Moreover, the VTA makes functional connections with the nucleus accumbens (NAc), striatum, and motor cortex (Mogenson et al., 1980; Hosp et al., 2011; Kunori et al., 2014; Beier et al., 2015), providing access to canonical locomotive control circuitry. Furthermore, glutamatergic projections seem to be a major component of these VTA-converging, locomotion-controlling pathways (Fuhrmann et al., 2015; Geisler and Wise, 2008). And despite the reviewed effects of MSDB glutamatergic stimulation on hippocampal-entorhinal speed encoding, recent investigation also suggests that these speed effects may be at least partially mediated by local glutamatergic projections onto other MSDB cell types projecting to the hippocampal-entorhinal complex (Fuhrmann et al., 2015; Robinson et al., 2016). These two lines of evidence suggest that the MSDB glutamatergic population may represent the segregators of the region's speed signal's distinct functions, sending speed-scaled output to locomotive circuitry while simultaneously transmitting an efference copy-like signal to the other MSDB cells to convey to the hippocampal-entorhinal complex for use in spatial representations and possible locomotive feedback.

Finally, while the contents of this review have for the most part intentionally avoided discussing any possible distinct encoding mechanisms for speed and acceleration, it should be noted that, while underreported relative to speed, acceleration-specific coding has indeed been reported (Kemere et al., 2013; Long et al., 2014). It has been further

suggested that acceleration, and not speed, may in fact dominate aspects of temporal

coding of movement (Long et al., 2014; Kropff Causa et al., unpublished), but further

experimentation is required to support this notion.

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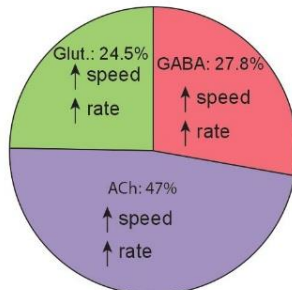
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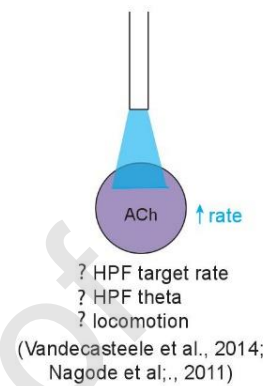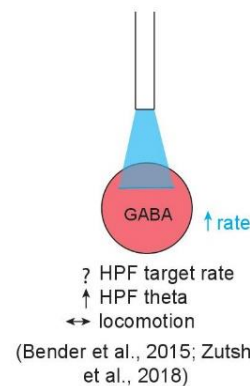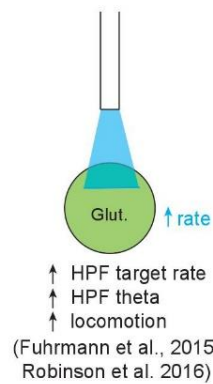
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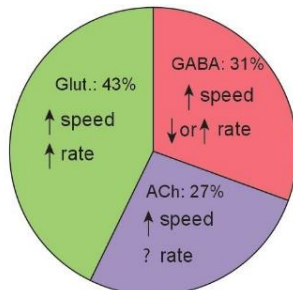
Figures:

(A) MSDB population proportions

Glut.: 24.5%
↑ speed
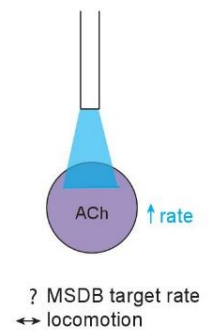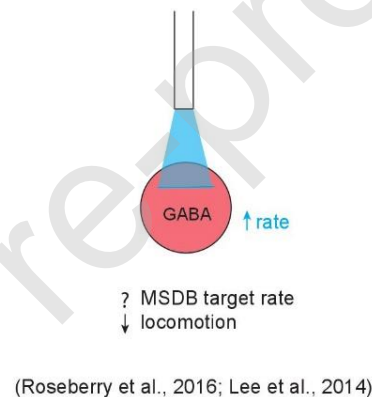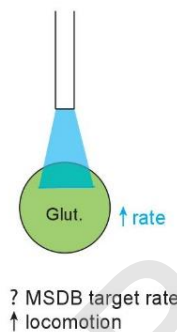↑ rate

GABA: 27.8%
↑ speed
↑ rate

ACh: 47%
↑ speed
↑ rate

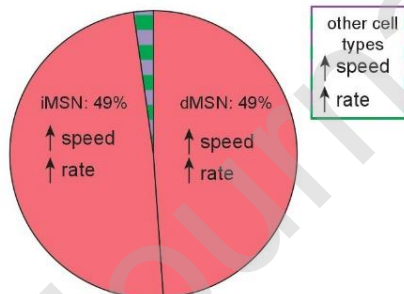(Colom et al., 2005; Fuhrmann et al., 2015; Justus et al., 2017; King et al., 1998; Davidson et al., unpublished)

Glut. ↑ rate
↑ HPF target rate
↑ HPF theta
↑ locomotion
(Fuhrmann et al., 2015; Robinson et al. 2016)

GABA ↑ rate
? HPF target rate
↑ HPF theta
↔ locomotion
(Bender et al., 2015; Zutshi et al., 2018)

ACh ↑ rate
? HPF target rate
? HPF theta
? locomotion
(Vandecasteele et al., 2014; Nagode et al;., 2011)

(B) MLR (PPN) population proportions

Glut.: 43%
↑ speed
↑ rate

GABA: 31%
↑ speed
↓ or ↑ rate

ACh: 27%
↑ speed
? rate

(Wang and Morales, 2009; Roseberry et al., 2016)

Glut. ↑ rate
? MSDB target rate
↑ locomotion

GABA ↑ rate
? MSDB target rate
↓ locomotion

ACh ↑ rate
? MSDB target rate
↔ locomotion

(Roseberry et al., 2016; Lee et al., 2014)

(C) BG (striatum) population proportions

iMSN: 49%
↑ speed
↑ rate

dMSN: 49%
↑ speed
↑ rate

other cell types
↑ speed
↑ rate

(Kreitzer and Malenka, 2008; Kim et al., 2014; Bartholomew et al., 2016)

dMSN ↑ rate
↑ MLR target rate
↑ locomotion

iMSN ↑ rate
↓ MLR target rate
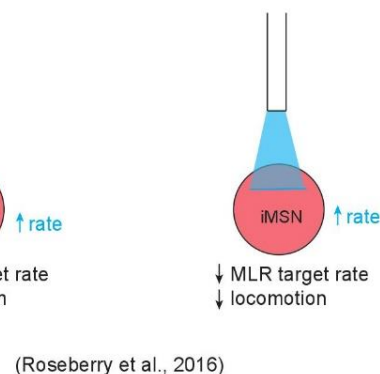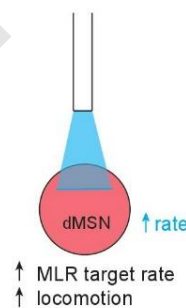↓ locomotion

(Roseberry et al., 2016)

<u>Figure 1</u>: Causal evidence for a speed circuit upstream of the hippocampal-entorhinal complex

A: The medial septum/diagonal band of Broca (MSDB) directly innervates the hippocampal formation ("HPF" in figure; Swanson and Cowan, 1979; Alonso and Köhler, 1984), while receiving projections from the mesencephalic locomotor region
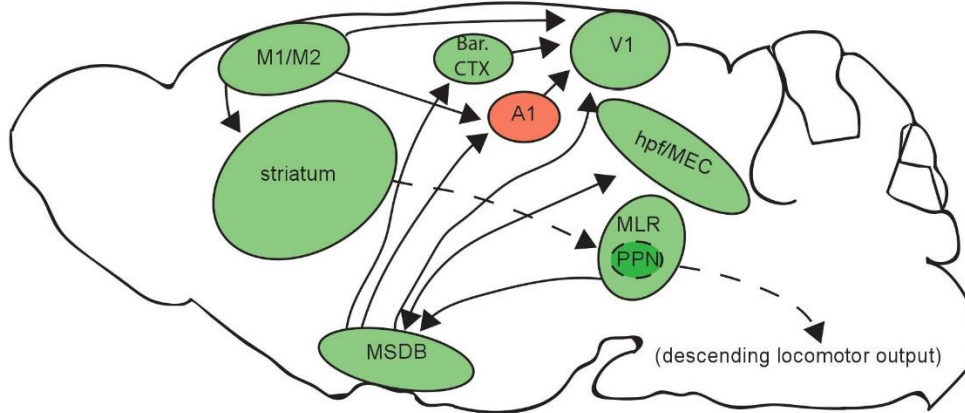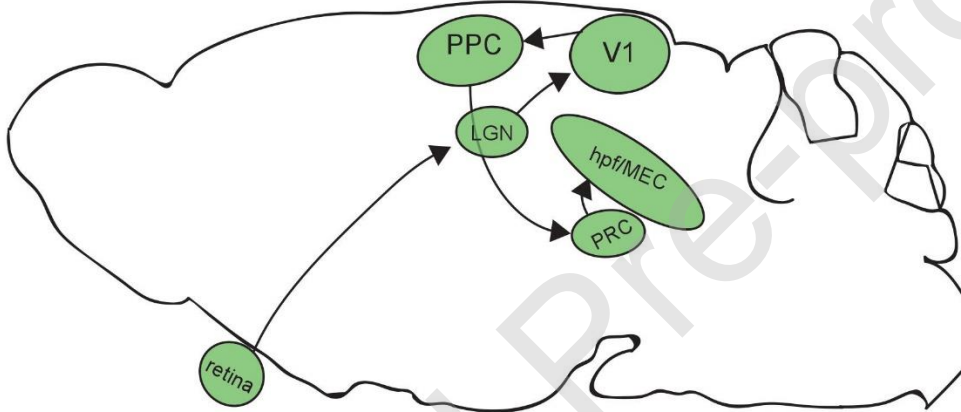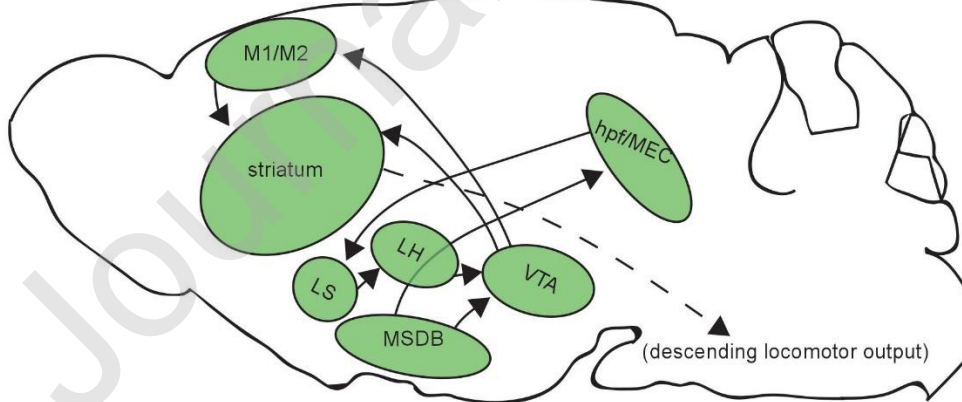
(MLR), and specifically two of its associated nuclei, the pedunculopontine tegmental nucleus (PPN) and cuneiform nucleus, among other regions (Nauta and Kuypers, 1958; Lee et al., 2014). The MSDB neuronal population is comprised of three major cell types: glutamatergic (Glut.) (24.5%), GABAergic (GABA) (27.8%), and cholinergic (ACh) (47%) (Colom et al., 2005). All three cell types can increase their firing rates with increased speed (Fuhrmann et al., 2015; Justus et al., 2017; King et al., 1998; Davidson et al., unpublished), although together, the MSDB population has been shown to have both positively and negatively speed-modulated activity (Justus et al., 2017). Optogenetic-mediated stimulation of glutamatergic and GABAergic cells can also influence rate and/or temporal coding in the hippocampal-entorhinal complex in a manner analogous to that of speed (Fuhrmann et al., 2015; Robinson et al., 2016; Bender et al., 2015), implicating these septo-hippocampal or septo-entorhinal projections in speed signal transmission, although recent evidence shows the glutamatergic effects may be primarily mediated by local stimulation of the other cell types (Robinson et al., 2016). The specific role of cholinergic projections in mediating downstream speed-like effects remains less well-defined, and indeed seems more complex in nature (Carpenter et al., 2017; Vandecasteele et al., 2014; Nagode et al., 2011). Interestingly, optogenetic activation of the MSDB glutamatergic population has also been shown to initiate locomotion and increase running speed (Fuhrmann et al., 2015).

B: The MLR is historically implicated in initiating and controlling locomotive behavior through its descending projections (Shik et al., 1966; Mori et al., 1978; Takakusaki, 2008), but also sends ascending projections to MSDB, among other regions (Nauta and Kuypers, 1958; Lee et al., 2014). It receives locomotion-associated input from the basal ganglia (Garcia-Rill 1986; Roseberry et al., 2016). The PPN population contains the same cell types as the MSDB population, albeit in different proportions (43% Glut., 31% GABA, 27% ACh) (Wang and Morales, 2009). Glutamatergic MLR cells scale their firing rates with running speed while GABAergic PPN cells show more heterogeneous responses to speed (Roseberry et al., 2016); the cholinergic population's rate-speed relationship has yet to be reported. Optogenetic activation of glutamatergic cells initiates locomotion and increases speed, while activation of GABAergic cells decreases speed and terminates locomotion (Roseberry et al., 2016). Activation of cholinergic cells seems to have minor effects on locomotion (Roseberry et al., 2016). Note that while the figure shows population proportions for PPN only, the optogenetic response results reflect a more general MLR population (Roseberry et al., 2016). While the MLR has been indirectly implicated in stimulating speed and locomotive signaling in MSDB and thus indirectly in the hippocampal-entorhinal complex (Lee et al., 2014; Fu et al., 2014), direct evidence for this relationship has only yet been reported in unpublished work (Carvalho et al., unpublished; Tanke et al., unpublished).

C: Basal ganglia cells also encode speed, particularly in the striatum (Kim et al., 2014; Bartholomew et al., 2016) and the substantia nigra (Barter et al., 2015). The basal ganglia has various monosynaptic outputs to the MLR (Garcia-Rill 1986; Roseberry et

al., 2016), and the PPN has been shown to project back to the striatum (Wall et al., 2013). A recent study (Roseberry et al., 2016) showed that medium spiny neurons in the direct (dMSNs) and indirect (iMSNs) striatal pathways increase their firing rates with speed and, furthermore, that optogenetic-mediated stimulation of these cells differentially controlled both running speed and MLR firing rates as depicted here.

(A) Circuits extracting speed information from motor input.

(B) Example circuit extracting speed information from sensory input.

(C) Circuits encoding speed that may also influence ongoing locomotion.

■ Speed enhances gain   ■ Speed decreases gain

Figure 2: Summary of known speed-related functional anatomy

Effects of speed on either rate or temporal codes have been reported in various interconnected brain regions that represent multiple, parallel, functional 'speed circuits'.

A: Circuits extracting speed information from motor input.
Speed signaling is extensive throughout the motor system, including in motor cortex (Leinweber et al., 2017; von Nicolai et al., 2014), striatum (see Fig. 1C), and the mesencephalic locomotor region (MLR) (see Fig. 1B). The MLR projects to the basal forebrain, including the medial septum/diagonal band of Broca (MSDB) (see Fig. 1), which itself projects the hippocampal-entorhinal complex in a manner that could logically produce a local motor-reflective speed signal (see Fig. 3). During locomotion, MSDB also transmits efference copy-like signals to various sensory cortices (Pinto et al., 2013; Fu et al., 2014; Lee et al., 2014) that are themselves interconnected (Fu et al., 2014) and contain various locomotive and/or speed signals (Fu et al., 2014; Pakan et al., 2016; Roth et al., 2016; Erisken et al., 2014; Saleem et al., 2013; Christensen and Pillow, 2017; Schneider et al., 2014; Chorev et al., 2016). Motor cortical areas, specifically M2, also provides these efference copies via direct innervation of the sensory areas (Schneider et al., 2014; Leinweber et al., 2017). While diverse speed codes are common throughout this circuitry, the only area that has only been reported to contain a consistently diminished network effect with speed and/or locomotion is auditory cortex (Schneider et al., 2014; Zhou et al., 2014).

B: Circuits extracting speed information from sensory input.
Sensory information may also reach the hippocampal-entorhinal complex to influence speed signaling via many putative circuits, at least one of which has consistently reported speed effects. The retina projects to the LGN and encodes information about optic flow speed. LGN cellular rates encode running speed (Roth et al., 2016; Erisken et al., 2014; but see Niell and Stryker, 2010), while this area serves as the primary source for visual information in visual cortex (Niell 2015). Running speed and locomotion more broadly seem to modulate processing in the visual cortex in a variety of ways, particularly in V1 (Fu et al., 2014; Pakan et al., 2016; Roth et al., 2016; Erisken et al., 2014; Saleem et al., 2013; Christensen and Pillow, 2017). Visual cortex in turn projects to the posterior parietal cortex (PPC) (Miller and Vogt, 1984), which has been recently reported to also contain a temporal speed signal (Yang et al., 2017). PPC next innervates the postrhinal cortex (PRC) (Burwell and Amaral, 1998), which displays similar speed modulation (Furtak et al., 2012). Finally, PRC innervates the hippocampal-entorhinal complex (Burwell and Amaral, 1998; Agster and Burwell, 2009).

C: Circuits encoding speed that may also influence ongoing locomotion.
Recent evidence has suggested that the relationship between MSDB, and possibly even hippocampal-entorhinal speed signaling and locomotive speed may in fact be bidirectional as it is in areas such as the MLR (Bender et al., 2015; Fuhrmann et al.,

2015; Vandecasteele et al., 2014, see Fig. 1). A few interconnected circuits have been hypothesized to provide the anatomical underpinnings for this possibility (Fuhrmann et al., 2015; Bender et al., 2015): MSDB projects directly to the ventral tegmental area (VTA) (Fuhrmann et al., 2015; Geisler and Wise, 2008), which in turn projects to various motor system areas, including motor cortex and the striatum (Mogenson et al., 1980; Hosp et al., 2011; Kunori et al., 2014; Beier et al., 2015). The hippocampal-entorhinal system may be able to utilize the same circuit to influence the ongoing locomotive state, through its projections to the lateral septum (LS) and the following LS-to-lateral hypothalamus (LH) projections (Bender et al., 2015; Geisler and Wise, 2008). Every area within these circuits have been reported to contain speed signals of some type (Zhou et al., 1999; Puryear et al., 2010; Wang and Tsien, 2011; Bender et al., 2015) and to induce locomotive changes upon direct stimulation (Fuhrmann et al., 2015; Kalivas et al., 1981; Parker and Sinnamon, 1983; Christopher and Butter, 1968; Patterson et al., 2015; Bender et al., 2015).