TITLE: Hippocampal sharp wave-ripple dynamics in NREM sleep encode motivation for anticipated physical activity

ABBREVIATED TITLE: (50-character maximum) Sharp wave-ripples encode motivation for future exercise

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CONFLICT OF INTEREST statement

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ABSTRACT:

Physical activity is an integral part of every mammal's daily life, and as a driver of Darwinian fitness, required coordinated evolution of the body and brain. Our species is in its most historically sedentary state, creating a global health crisis - necessitating understanding of exercise motivation. The decision to engage in physical activity is driven by survival needs or by motivation for the rewarding nature of physical activity itself. Rodents exhibit innate and learned motivation for voluntary wheel running, and over time run longer and farther, reflecting increased incentive salience and motivation for this consummatory behavior. Daily motivation for running is variable, requiring dynamic coordination of neural and somatic physiology (e.g., motivation for an anticipated experience and associated metabolic demand) to successfully carry out the planned activity. Hippocampal sharp wave-ripples (SWRs) evolved both cognitive and metabolic functions, which in modern mammals likely facilitates body-brain coordination. Here we monitored hippocampal CA1 SWRs and running in adult mice, while manipulating the incentive salience of running. During non-REM (NREM) sleep, the duration of SWRs before (but not after) running positively correlated with future running duration. In contrast, the rate of SWRs before and after were positively correlated with running duration. Long SWRs reflect activation of larger cell assemblies (i.e., more information), while SWR rate reflects both information and metabolic signaling. Our results thus suggest that multiplexing of SWR dynamics is a mechanism supporting cognitive and metabolic facets of behavior. We hypothesize that SWRs coordinate body-brain interactions to a greater extent than previously known.

KEYWORDS: exercise; physical activity; voluntary wheel running; hippocampus; CA1; sharp wave-ripples; learning; memory; motivation; anticipation; reward; planning; incentive salience; metabolism; embodiment; sleep

SIGNIFICANCE STATEMENT:

Darwinian fitness is increased by body-brain coordination, though neural substrates are poorly understood. Specific hippocampal rhythms (i.e., CA1 SWRs), which have a well-established role in reward learning, action planning and memory consolidation, have also been shown to modulate systemic [glucose]. Using a mouse model of voluntary physical activity that requires body-brain coordination, we monitored SWR dynamics when animals were highly motivated and anticipated rewarding exercise (i.e., when body-brain coordination is of heightened importance). We found that during non-REM sleep before exercise, SWR dynamics (which reflect cognitive and metabolic functions) were correlated with future time spent exercising. This suggests that SWRs support cognitive and metabolic facets of behavior by coordinating the body and brain.

Introduction

Throughout mammalian evolution, physical activity has been a significant driver of Darwinian fitness, with the body and brain co-evolving, concomitantly increasing in complexity at the level of structure and function (Hill and Polk 2019). As spatial navigation behaviors increased, the concurrent need to learn and remember the environment did as well, enhancing success in foraging and reproduction (Raichlen and Alexander 2017). Today however, physical inactivity in humans has become a global health crisis (Santos et al. 2023), with sedentary behaviors increasing the risk for a range of health issues including obesity, diabetes, heart disease, stroke, and cancer (I.-M. Lee et al. 2012). Conversely, physical activity improves physical and mental health (Sharma, Madaan, and Petty 2006), making understanding exercise motivation a critical and timely scientific and societal issue.

The hippocampus is functionally positioned to play an important yet relatively unexplored role in exercise motivation, as it supports learning and memory (Eichenbaum 2017) (including reward learning), planning of future actions (Johnson and Redish 2007; Diba and Buzsáki 2007; Foster and Wilson 2006; György Buzsáki 2015; Pastalkova et al. 2008) and although less acknowledged is involved in somatic physiology (Kanoski and Grill 2017; Shimazu 1987; Tingley et al. 2021) . Critical to all of these functions are CA1 sharp wave-ripples (SWRs) (György Buzsáki 2015), during which specific populations (i.e., cell assemblies) of CA1 neurons become highly active (Diba and Buzsáki 2007; Foster and Wilson 2006; Nádasdy et al. 1999; A. K. Lee and Wilson 2002; Dragoi 2020), selected by computations involving interaction between excitation and inhibition (György Buzsáki 2015; Daniel F. English et al. 2014; Stark et al. 2014), sending the final product

of hippocampal computation to the rest of the brain (György Buzsáki 2015; Nitzan et al. 2020; Karimi Abadchi et al. 2020; G. Buzsáki 1989). Interestingly, recent findings have shown that in addition to cognitive functions (largely involving hippocampal-neocortical dialogue), SWRs serve a specific somatic function: dynamically regulating peripheral glucose levels by communicating with the lateral septum (Tingley et al. 2021). The differential translation of hippocampal SWR output by neocortex (A. K. Lee and Wilson 2002; Karimi Abadchi et al. 2020; G. Buzsáki 1989; G. Buzsáki et al. 1992; Girardeau et al. 2009; van de Ven et al. 2016; Trouche et al. 2016) and lateral septum (Tingley et al. 2021; Tingley and Buzsáki 2018) may thus enable multiplexing of cognitive and somatic functions. Furthermore, multiple hippocampal rhythms including SWR and theta are entrained to and driven by respiration (Karalis and Sirota 2022; Lockmann et al. 2016; Nguyen Chi et al. 2016; Yanovsky et al. 2014), furthering the evidence of the important somatic/metabolic role of SWRs. Considering these dynamic roles of SWRs as modulators between the body and brain, we hypothesized that SWRs serve essential functions in behaviors that require enhanced body-brain coordination including physical activity.

The decision to engage in physical activity can be driven by survival needs (e.g., escaping danger) or by the motivation for the rewarding nature of physical activity itself (e.g., running exercise). Physical activity, in the form of voluntary (but not forced) wheel running, holds positive incentive salience for rodents (Basso and Morrell 2017; Brené et al. 2007; Greenwood et al. 2011). Critically, motivation for wheel running exercise can be quantified through the magnitude of the rebound running response after days of wheel deprivation (Basso and Morrell 2015). We thus investigated dynamics of SWRs during

NREM sleep in a rodent model exhibiting high levels of motivation for this behavior (Sloin et al. 2022). We monitored hippocampal local field potentials (LFP) before, during, and after two hours of voluntary exercise; both on consecutive days and after days of wheel deprivation (deprivation increases incentive salience and thus running levels) (Basso and Morrell 2017). Differences in daily motivation to run were associated with changes in sleep architecture and SWR dynamics including rates and durations. These results suggest a previously unknown role for SWRs in the motivation for physical activity.

Materials and Methods

Experimental considerations: For all experiments, we utilized four exercise naïve F1 BL/6J x FVB/NJ hybrid female mice bred in our colony. This mouse strain was utilized as previous work (Sloin et al. 2022) has demonstrated high levels of cognitive functioning and low levels of anxiety compared to typical monogenic strains (e.g., C57), making them a more ethologically relevant model to study innate behaviors such as physical activity. Considering that this study focused on the motivation for voluntary exercise, we intentionally chose to use females, as the voluntary wheel running distances and rates are 1.5 times that of male, females run more consistently across the lifespan and have higher mean levels of physical activity (Basso and Morrell 2017) , particularly at the adult timepoints we are studying. To limit inter-animal variability in both physiology and behavior, all animals were housed identically, and recordings and behavioral tasks were completed in the same behavioral testing rooms at the same time of day to insure that observed variabilities were not due to location or circadian rhythms. To minimize effects of age, young adult mice (~PND 60) were used for this study, as wheel running is most robust during this time period. All mice received *ad libitum* food and water, as food

and/or water deprivation have been shown to alter wheel running patterns(Hall and Hanford 1954). Finally, room temperatures, light/dark cycles, noise level, and odors were monitored and kept constant to eliminate any additional stressors. All procedures were approved by the Institutional Animal Care and Use Committee at Virginia Tech.

Behavioral task: We utilized the Sleep Run Sleep (SRS) protocol for measuring hippocampal activity and exercise behaviors*.* The SRS protocol was developed to measure hippocampal LFP biomarkers in the context of acute exercise experience. Under the SRS protocol (fig 1A), exercise-naïve female BL/6J x FVB/NJ mice were chronically implanted with a 64-channel silicon probe (Cambridge Neurotech) spanning the hippocampus from the CA1 through the dentate gyrus granular cell layer at 10–12 weeks old. Following surgical recovery, baseline recordings were made in the home cage to habituate mice to the recording procedures. Under the SRS protocol, neural activity is recorded throughout behavioral tests and sleep sessions; this protocol therefore enabled us to examine sleep architecture and signaling before and after behavior. These recordings were obtained during the animal's light cycle to ensure the capture of substantive sleep physiology. The SRS protocol begins with 90 minutes of sleep in the home cage, followed by 2 hours of running wheel access in a novel cage, and ending with another 90 minutes of sleep in the home cage. The LFP was recorded continuously and synchronized with video of the running phase activity. Following the collection of baseline sleep activity, we collected 7 days of consecutive SRS recordings to examine effects across time. Due to neophobia, we found that between animals there was variability in interactions with the wheel on the first two days that stabilized by day 3. Therefore, we only considered data from day 3 and after in our analyses. Two rebound-SRS recordings

were collected 7 and 14 days after the last consecutive day to examine rebound running behaviors and hippocampal activity during different motivational states. Running behaviors were analyzed using the MedAssociates, Inc. low-profile wireless running wheel for mice (ENV-047) and wheel running software, as well as manual scoring for total duration of running (seconds) per running phase. Overall, the SRS protocol (informed by our previous work on exercise motivation) allowed us to examine hippocampal physiology during both the initial phase of consecutive-day running and the rebound running response phase on days after deprivation (Basso and Morrell 2015).

Chronic Hippocampal Extracellular recordings in freely behaving mice: Mice (N=4) were chronically implanted with 64-channel linear silicon probes (Cambridge NeuroTech) across the hippocampus, a described in (English et al, 2017). Briefly, probes were mounted on custom microdrives secured to the skull with dental cement, and subsequently inserted into the brain through a single craniotomy located at –1.75 AP and 1 ML in reference to bregma. A 50 μm stainless steel ground wire was implanted between the skull and dura over the cerebellum. This configuration allowed us to record electrical activity over >1 mm with 20-micron resolution and identify anatomically localized activity across the dentate gyrus (DG) and CA regions. Recordings were obtained using a digital multiplexing amplifier (Intan Technologies LLC) sampled at 30 kHz and synchronized with overhead video.

Figure acknowledgements: Figure 1B was made with images from the Allen mouse brain atlas. Figures 1 and 2 contain images from BioRender.com.

Analysis of Local Field Potentials: Analysis was performed using custom MATLAB scripts including those based on freely available functions from the Buzcode toolbox https://github.com/buzsakilab/buzcode.

Theta power: Mean theta (7-11 Hz) power is computed using freely available functions from the FMAtoolbox (MTSpectrogram and SpectrogramBands).

Ripple Detection: Ripple Detection was performed using standard algorithms as we have previously published (Daniel F. English et al. 2014; Daniel Fine English et al. 2017).

State Scoring: Segmentation of data into brain states (i.e., Wake, REM, NREM) was performed using previous methods (Watson et al. 2016). Briefly, periods of each state were segregated based upon a combination of characteristic features of LFP and EMG activity, followed by manual curation using accelerometer data to validate state scoring.

Statistics: All statistical analyses were performed in MATLAB (MathWorks). We observed highly variable behavior on the first and/or second days in different animals (data not shown), which were no longer present by day 3, as such statistical analyses are restricted to day 3 forward with the exclusion of days in which sleep was not captured within resting epochs. Considering that significant inter-individual variability in running distance/duration was observed, we normalized wheel running duration within animals (% of max running duration = daily duration/maximum daily duration), and cross-validated normalization procedures to make accurate and robust quantification of exercise. Note, the maximum daily duration that was used to normalize running behaviors was taken across all experimental days to establish an individual exercise performance scale. We

investigate the relationship of daily wheel running behaviors to all variables of interest (e.g., SWR rate and duration) by computing the Pearson's linear correlation coefficient and p-values using a student's t distribution for a transformation of the correlation. All correlations contain 27 data points from N=4 mice (one day is omitted because there was no NREM sleep in Pre).

Results

Plastic motivation for voluntary wheel running in BL/6J x FVB/NJ hybrid mice chronically implanted with silicon probes

To identify relationships between voluntary physical activity and hippocampal network oscillations we monitored wheel running (Fig 1A) and hippocampal extracellular field potentials (Fig 1B) in freely behaving mice under the SRS protocol (Fig 1A). Hybrid mice (Sloin et al. 2022) were chosen because they are a more ethologically relevant model compared to inbred strains. We analyzed data only from days after which the wheel running experience was no longer novel (i.e., day 3 and on) because novelty generally produces variability in behavior across animals, and specifically alters SWR dynamics (Diba and Buzsáki 2007; Foster and Wilson 2006; György Buzsáki 2015; Nádasdy et al. 1999; A. K. Lee and Wilson 2002; de la Prida 2020)(also see Methods). Time spent running increased over days (Fig 1D; $r = 0.59$, $p = 0.001$), and deprivation resulted in a subsequent rebound response upon return of the wheel (Fig 1C; $t(3) = -3.798$, $p = 0.032$), confirming mice found wheel running rewarding. We observed canonical relationships between behavioral states and hippocampal oscillations (György Buzsáki 2015; G. Buzsáki 1989; György Buzsáki 2002): theta oscillations were most prevalent in wake and REM sleep, whereas SWRs were most prevalent in NREM sleep. Importantly, wheel

running bouts were accompanied by sustained theta oscillations, resulting in a positive correlation between theta power and time spent running. (Fig 1E; r = 0.68, p=0.001). The SRS protocol thus meets the need of our study in that mice chronically implanted with silicon probes exhibit normal exercise behaviors and hippocampal activity.

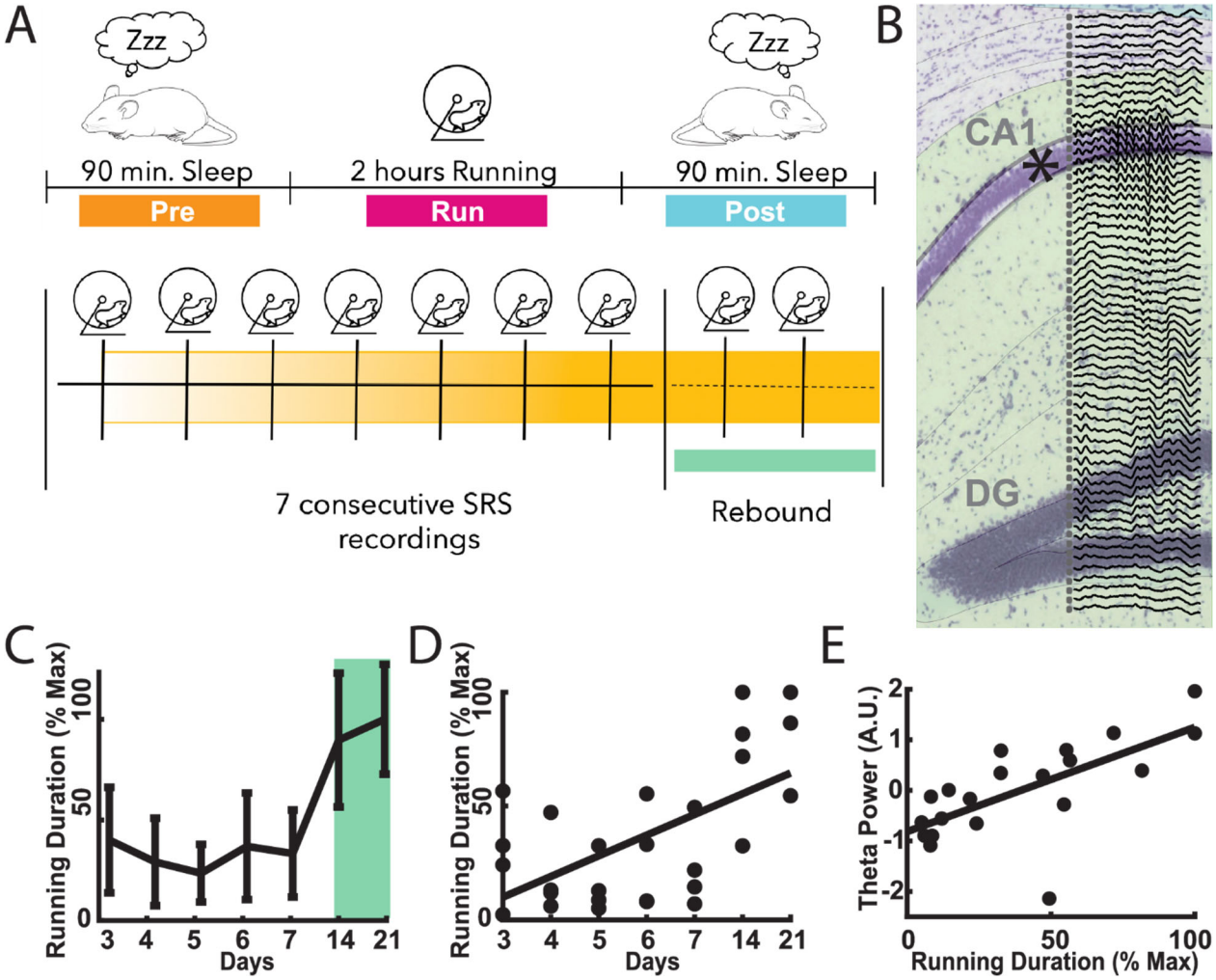

Figure 1: Motivation behaviors and hippocampal physiology in exercising mice

A. Behavioral Protocol. **B.** Example silicon probe recording CA1-DG 64 channel probe with 20 micron spacing implanted during SRS protocol. LFP traces are 150 ms illustrating a SWR event. **C.** Mean running duration on consecutive and rebound days. (t(3)=-3.798, p=0.032) **D.** Running over Days (r= 0.59,p= 0.001) **E.** Hippocampal theta correlates with running duration (r= 0.68, p=0.001). Each point is data from a single day. N=4 mice.

Anticipation of rewarding exercise results in increased wakefulness and compressed NREM sleep

We quantified relative time spent in different sleep/wake states using established methods (Watson et al. 2016), Fig 2A, and found that on rebound days mice spent significantly more time awake in Pre as compared to *Post* exercise epochs (p=0.01). We found the opposite relationship for NREM sleep, and over days the percent time in NREM in Pre epochs was negatively correlated with future time spent running (Fig 2C; r=-.676, p=0.0001). The opposite was true for NREM in *Post* epochs (Fig 2D; r=.426 p=0.026). Intriguingly, in Pre there is a significant negative correlation between SWR rates and the % time spent in NREM sleep (r=-0.6337, p= 0.0003), as well as significant negative correlations between inter-SWR-interval (ISI) and future time spent running (r=-0.50899, p=0.006), suggesting an anticipation driven compression of required SWR mediated computations into a shorter duration of time. This was not the case for the *Post* epoch correlations between ISI and running duration (r=-0.37591, p=0.0533) or SWR rates and the % time spent in NREM (r=0.363, p=0.06). Thus, periods of increased running were preceded, but not followed, by compressed NREM sleep.

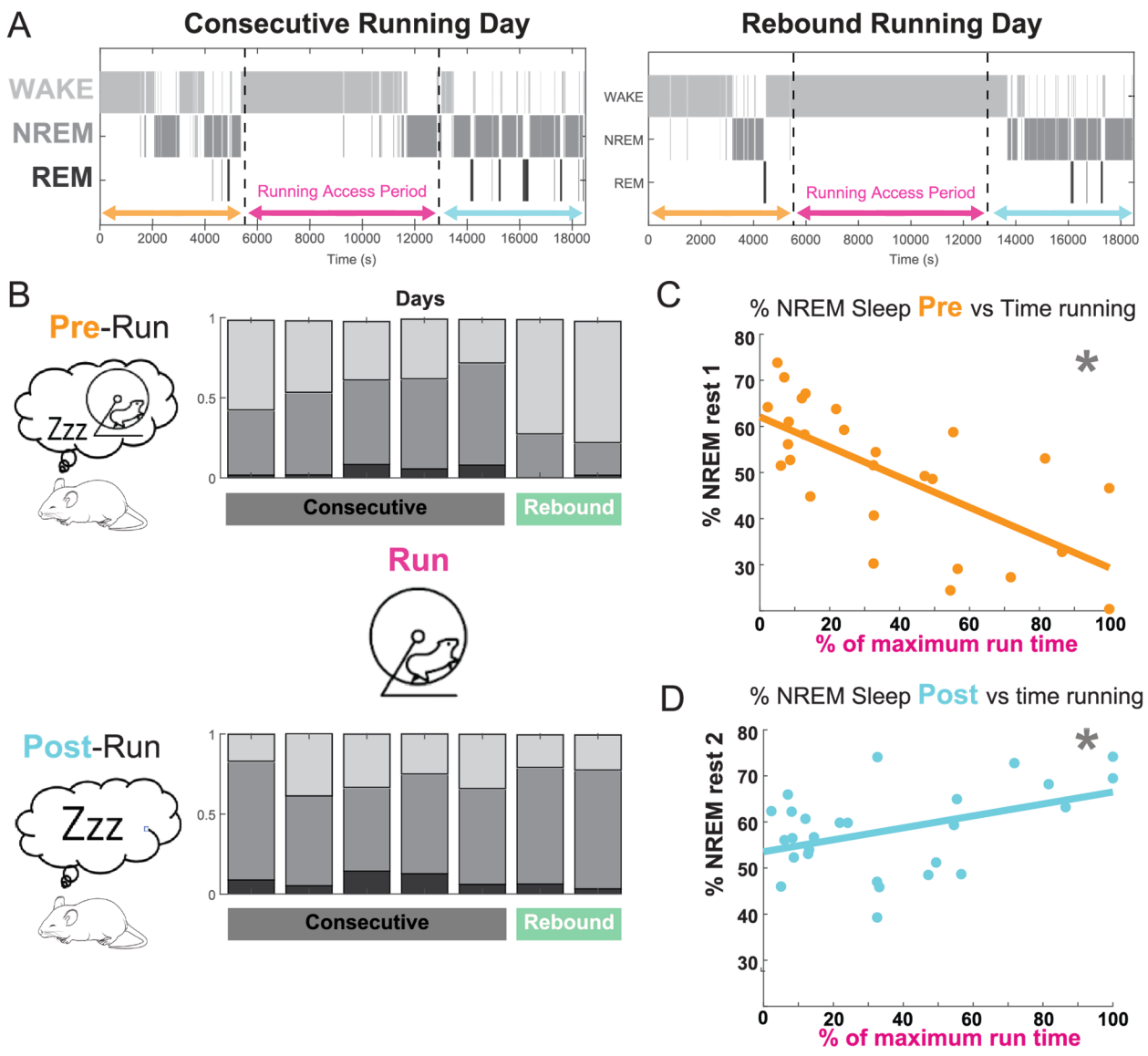

Figure 2: Alterations in wake/sleep dynamics associated with exercise motivation

A. Representative hypnograms of a consecutive day and a rebound day, for the entire period of recording. Note the differences between NREM in Pre on the consecutive and rebound day. Also note that on rebound day the mouse was awake the entire period with the wheel, which is not the case on the consecutive day. **B.** Summary figure of the proportion of time spent in wake, NREM and REM states in Pre (top) and Post (bottom) on consecutive and rebound days for one mouse. **C.** Correlation between running and the percentage of time spent in NREM sleep during Pre (r=-.676, p=0.0001) **D.** Correlation between running and the percentage of time spent in NREM sleep during Post (r=.426 p=0.026). Each point is data from a single day. 27 data points per correlation. N=4 mice.

SWR rates correlate with daily exercise performance

We compared SWRs in NREM sleep in *Pre* and *Post* run epochs in adult female mice. Neither SWR mean power or frequency exhibited significant correlations with exercise levels (data not shown). Rates and durations of SWRs, however, were related to daily exercise levels (Fig 3 & 4). NREM SWR rates in both *Pre* and *Post* epochs were positively correlated with daily running levels (Fig 3: A, B). The differences in SWR rate (Pre-Post) are also positively correlated with daily running performance (Fig 3: C). Examined together these relationships between SWR rate and running performance (Fig 3: A, B, C) indicate that SWR rate may be related to the daily energy expenditure of the animals.

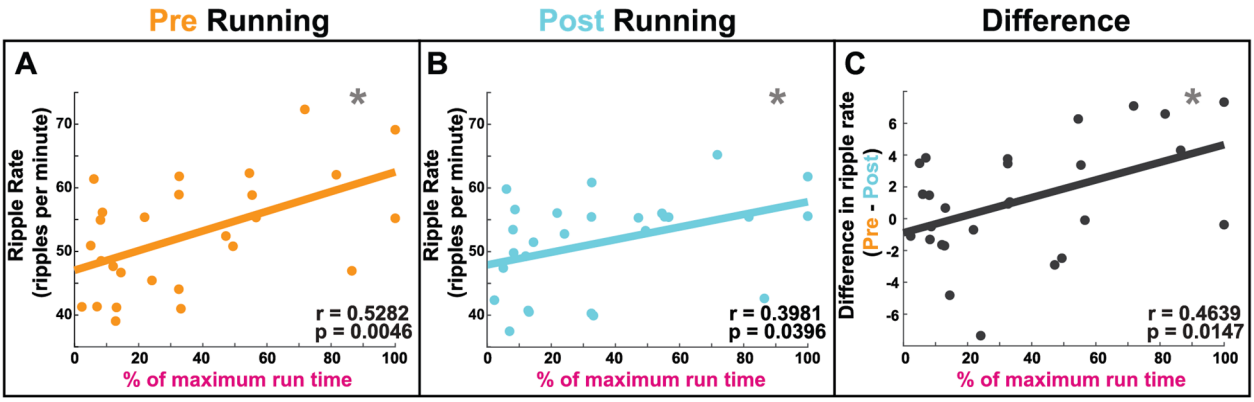

Figure 3: SWR Rate correlates with physical activity.

SWR rate (ripples per minute) in Pre and Post NREM sleep correlates with time spent running. **A.** In Pre SWR rate significantly correlates with time spent running. **B.** In Post SWR rate significantly correlates with time spent running. **C.** The difference between SWR rate (Pre – Post) significantly correlates with time spent running. Each point is data from a single day. 27 data points per correlation. N=4 mice.

SWR durations correlate with future exercise levels

SWR <u>durations</u> in *Pre* NREM were significantly positively correlated with future exercise levels which was not observed in *Post* NREM epochs (Fig 4: A, B, C). In parallel, the percent of long duration (Fernández-Ruiz et al. 2019) SWRs were significantly

positively correlated with future exercise levels in *Pre* but not *Post* (Fig 4: D, E, F). These data suggest that SWRs dynamically encode the motivation for anticipated exercise.

To determine if the increased rate in SWRs was related to the observed changes in duration we calculated the correlation between these variables in the Pre running period, finding no significant relationship (r = -0.05, p = 0.81). Importantly, this suggests that distinct physiological mechanisms underlie changes in rate and duration of SWRs. Additionally, this confirms that the SWR detection does not trivially reveal more long duration ripples as a function of SWR rate.

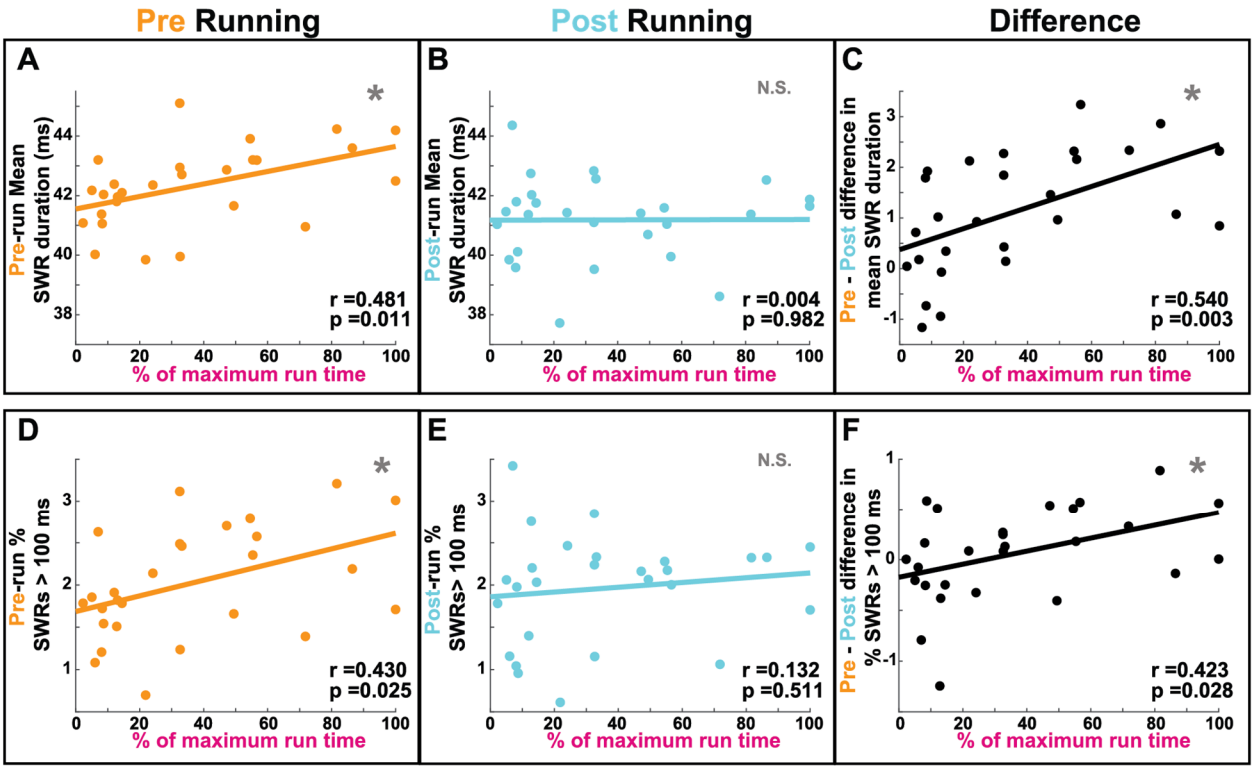

Figure 4: SWR Durations correlate with future physical activity.

Sharp wave-ripple duration in Pre but not Post NREM sleep is correlated with time spent running. Relationships between Pre and Post run SWR duration (A, B,C) or percent of long duration SWRs (D,E,F) and time spent running. Note that SWR activity before but not after running, as well as the differences between these timepoints, are both significantly positively correlated with time spent running each day. Each point is data from a single day. 27 data points per correlation. N=4 mice.

Discussion

Running is a naturally rewarding consummatory behavior

Our data demonstrate that running is a rewarding behavior in mice. First, we demonstrated that mice increase their running over days. Second, we found that mice exhibit the rebound running response after deprivation, previously only shown in rats (Basso and Morrell 2017; 2015). Interestingly, this behavior was observed after only 7 days of acute running experience, while previous studies in rats reported that this behavior only occurs after habitual plateau levels of running are reached (Basso and Morrell 2017; 2015). Specifically, rebound running distance and rates on days 14 and 21 reached peak levels, above those demonstrated on the final consecutive day of running (day 7). This phenomenon is akin to what occurs after deprivation from other natural or pharmacological reinforcers such as food or drugs of abuse. To this point, we previously used a conditioned place preference model to show that running can be as rewarding as cocaine (Basso and Morrell 2015). These new findings demonstrate that motivation comes on board with only 7 days of consummatory behavior of wheel running experiences.

Furthermore, it is important to note that from the perspective of hippocampal rhythms, consummatory behaviors are typically associated with a cessation of theta oscillations and the occurrence of SWRs, however, exercise (Basso and Morrell 2017; Brené et al. 2007; Greenwood et al. 2011; Basso and Morrell 2015) and sex (Kurtz 1975; Kurtz and Adler 1973) are two prominent examples of innately rewarding consummatory behaviors which are associated not with SWRs but with sustained theta oscillations.

Exercise modulates sleep architecture during anticipation of the running experience

When mice are anticipating the reward of running, they spend more time awake and less time asleep, with this effect being most prominent during rebound days to the point where some mice spend nearly their entire anticipatory period awake (Fig.2 A, B). Additionally, when mice fall asleep during this anticipatory period, they spend the majority of their time in NREM sleep with the percentage of NREM sleep negatively correlating to the time spent running (Fig 2C). That is, the more the mouse is motivated to run, the more time they spend awake and the less time they spend in NREM sleep before running. However, after the running experience, high levels of exercise motivation (i.e., time spent running) correspond to more NREM sleep (Fig. 2D). This latter finding is consistent with the human literature showing that both acute (a single bout) and chronic exercise produces longer periods of NREM sleep and shorter periods of REM sleep (Uchida et al. 2012). Additionally, extant literature has revealed that exercise enhances overall quality of sleep including shorter sleep onset latency (Kubitz et al. 1996), time awake after sleep onset and longer total sleep time (Youngstedt, O'Connor, and Dishman 1997). We newly show that during an anticipatory running period, mice will regulate their sleep-wake cycles (Fig 2). That is, the external signal that the experience of running will soon be available alters the circadian pattern of the rodent such that awake periods are more prominent prior to (as compared to after) the running experience. Other literature has shown that such learned responses (e.g., food becoming available at a certain time of day) can alter circadian responses of other consummatory behaviors such as eating/feeding (SILVER and BALSAM 2010). Our findings reveal a general phenomenon regarding entrainment

of innate behaviors (including physical activity and sleep), and that the timing of when these events occur in relation to one another can affect the temporal relationship of said behaviors.

SWR dynamics encode exercise motivation and performance

SWRs are commonly studied using metrics including oscillation frequency, power, event duration, rate, and (ISI). We found that SWR frequency and power were not related to exercise behaviors, as expected since SWR frequency is in general fixed across and during learning and memory tasks (György Buzsáki 2015), with changes in frequency being associated with pathological states (György Buzsáki 2015; Valero et al. 2017; Ibarz et al. 2010). In contrast, duration, rate, and ISI demonstrated unique relationships with exercise motivation and performance which suggest a role for SWRs in multiple aspects of exercise behaviors. Of note, in both rate and durations, all correlations were stronger for *Pre* as compared to *Post,* with the differences in rates (*Pre* - *Post*) showing positive correlation with exercise levels, suggesting potential anticipatory functions for both SWR rates and durations. The discrimination between rate and duration of SWRs is paramount, as distinct functions have been ascribed to modulations of each metric. Critically, increased SWR duration is driven by the participation of more neurons in larger cell assemblies (carrying more information). As such, dynamic SWR duration may enable flexible encoding of cognitive aspects of motivation, while SWR rate modulation may be more of an anticipatory metabolic signal. In any case, these results suggest that the spiking content of SWRs is directly related to the anticipated and rewarding future exercise.

Conclusions

We identified a novel role for SWRs in coordinating neuronal and physical activity: encoding motivation for future exercise in the activity of CA1 cell assemblies in SWRs. This suggests that both motor and cognitive processes are integrated within the same neuronal circuits - evidence for embodied cognition (i.e., the embodied brain). This perspective may help to reconcile the dichotomous theories of the hippocampus as a spatial map versus the seat of learning and memory. The hippocampus may thus be a core embodied center of the brain supporting somatic and cognitive processes, as well as their coordination through time. This perspective directly aligns with the co-evolution of the body and brain (György Buzsáki and Tingley 2023) .

Importantly these results are novel and separate from SWR preplay (Dragoi and Tonegawa 2011) and replay (Diba and Buzsáki 2007; Foster and Wilson 2006; Nádasdy et al. 1999; A. K. Lee and Wilson 2002). These concepts regard the structure of pre-existing and/or learned spatial maps. Our results instead introduce the novel concept that cell assembly dynamics in NREM SWRs encode a plastic representation of the motivation for a future innate consummatory behavior. We further hypothesize that incepting such activity could be used as a method to increase exercise motivation and performance.

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