Brain activity is not only for thinking
Timothy O Laumann¹ and Abraham Z Snyder²,³

The human brain is a complex organ with multiple competing imperatives. It must perceive and interpret the world, incorporate new information, and maintain its functional integrity over the lifespan. Neural activity is associated with all of these processes. Spontaneous BOLD signals have been invoked as representing neural activity associated with all of these processes. However, their exact role in these processes remains controversial. Here, we review learning machine theory, molecular mechanisms of synaptic plasticity and homeostasis, and recent experimental evidence to suggest that spontaneous BOLD activity may be more closely aligned with off-line plasticity and homeostatic processes than on-line fluctuations in cognitive content.

Addresses
¹ Department of Psychiatry, Washington University in St. Louis School of Medicine, United States
² Department of Neurology, Washington University in St. Louis School of Medicine, United States
³ Department of Radiology, Washington University in St. Louis School of Medicine, United States

Corresponding author: Laumann, Timothy O (laumannl@wustl.edu)

Introduction
The existence of unceasing spontaneous brain activity has been recognized since at least the 1930s [1]. However, the functions of this activity have remained mysterious [2]. Over the last three decades, blood oxygen level dependent (BOLD) fMRI has become the dominant tool for measurement of brain activity in humans. Soon after the adoption of fMRI, it was observed that fMRI signals exhibit constant fluctuations unrelated to the task [3]. In the context of task fMRI, this activity was conventionally regarded as ‘physiological noise’ [4]. However, it is now clear that this ‘physiological noise’ is temporally correlated within functional systems [5,6]. It is this property of spontaneous brain activity that constitutes the basis of resting state functional connectivity (RSFC) [7]. The existence of this well-structured organization implies that spontaneous brain activity is physiologically consequential.

The meaning of spontaneous BOLD signal fluctuations has been variably interpreted along two different perspectives. According to one view, spontaneous BOLD fluctuations are proposed to reflect unconstrained cognitive processes, for example, retrospection, prospection, reflection, environmental monitoring — the ‘stream of consciousness’ — attendant to our subjective experience. Given the centrality of perception and action to mental life, it is appealing to assume that all observed brain activity is directly related to moment-to-moment cognition and behavior. This perspective has been reinforced by a massive accumulation of PET and fMRI experiments in which brain activity has been imaged with the objective of localizing cognitive operations [8]. More recently, the observation of ‘dynamic’ functional connectivity during wakeful rest and changes in functional connectivity between rest and task states have, at times, been interpreted as reflecting cognition [9,10].

We have previously articulated several problems with the notion that all ongoing BOLD activity directly reflects cognition and behavior (Box 1; [11]): (1) The topography of BOLD fMRI correlations remains largely intact during slow-wave sleep [12] and even anesthesia [13], states in which cognition is presumed to be either absent or greatly attenuated; (2) The extent to which task paradigms modify the correlation structure of spontaneous BOLD signal fluctuations is very limited [14,15,16]; (3) While unconstrained cognition might be expected to vary from scan to scan within an individual, RSFC remains remarkably consistent across sessions [17,18]. RSFC is also relatively stable within a given scan, discounting fluctuations attributable to drowsiness [11] or arousal [19], which likely relate to fluctuations in BOLD signals, at least partly due to alterations in respiratory behavior and pCO2 [20]. Moreover, brain metabolic activity is high at all times and minimally affected by task performance [21].

For all of these reasons, unconstrained cognition does not fully explain ongoing spontaneous activity. An alternative view proposes that spontaneous BOLD activity may more closely relate to mechanisms associated with learning and memory [22,23]. In the following, we review prior literature supporting the perspective that a substantial fraction of spontaneous brain activity represents homeostatic and consolidative signaling, the function of which is to enable neural plasticity while maintaining the brain’s functional integrity through time. We also review recent
Box 1 Evidence that RSFC structure is largely independent of cognitive content

1. RSFC structure is similar during wake and sleep. For instance, DMN structure is observed through wake, S1, S2, and SWS [12,100].
2. RSFC structure is present under anesthesia [13,101], although covariance does diminish with increased sedation [102].
3. RSFC structure is minimally altered by task state [14–16].
4. RSFC structure within subject is consistent across sessions [16,11,103].
5. RSFC structure within subject is similar over long time scales [18,17].
6. RSFC structure is consistent across subjects at the population level [104,105].
7. Similar RSFC structure is evident across mammalian species [106–108].

Brain activity is not only for thinking

Laumann and Snyder 131

Brain activity is not only for thinking

Laumann and Snyder 131

Box 1 Evidence that RSFC structure is largely independent of cognitive content

1. RSFC structure is similar during wake and sleep. For instance, DMN structure is observed through wake, S1, S2, and SWS [12,100].
2. RSFC structure is present under anesthesia [13,101], although covariance does diminish with increased sedation [102].
3. RSFC structure is minimally altered by task state [14–16].
4. RSFC structure within subject is consistent across sessions [16,11,103].
5. RSFC structure within subject is similar over long time scales [18,17].
6. RSFC structure is consistent across subjects at the population level [104,105].
7. Similar RSFC structure is evident across mammalian species [106–108].

evidence that BOLD RSFC may be intimately tied to these processes.

Learning machine theory

When considering the role of ongoing neural activity in brain function, it is important to recognize that one of the brain’s primary capacities is its ability to learn new information about its environment. Theoretical considerations, initially formulated by David Marr [24], suggest that any associative learning machine functions optimally if it is allowed to alternate between two states: (1) a learning phase, during which the machine is connected to inputs and connections are enhanced between simultaneously active elements and (2) a restorative phase during which the machine is disconnected from inputs and connections between elements are rebalanced in a manner that increases randomness (entropy) [25,26]. In multi-layer perceptrons, this principle is expressed as iterational alternation between a forward phase, during which prediction error is evaluated, and a backward phase, during which connection weights are adjusted by back-propagation [27]. The starkest expression of the state alternation principle in living organisms is sleep versus wake. This alternation appears to be necessary: all organisms capable of learning alternate between wake versus sleep states [28]. In vertebrates, events experienced during wake are registered in the hippocampus and the cerebral cortex [29,30]. During slow wave sleep (SWS), reactivation of the same circuits leads to the creation of stable (consolidated) episodic memory [31].

Understanding how state alternation is implemented in brains requires consideration of the cellular and molecular events underlying synaptic weight modification. Activity-dependent synaptic plasticity plays a crucial role in brain development well before birth [32–34]. For example, retino-tectal connections have been shown to be sculpted by spontaneous retinal waves during prenatal development of the visual system [35]. Following birth, spontaneous activity continues to refine neural connections using sensory feedback [36,37]. During early life critical periods, experience-dependent synaptic plasticity tunes the response properties of cortical sensory neurons (e.g. ocular dominance columns) [38]. As the brain matures, metabolic ‘brakes’ limit neural plasticity to mechanisms centered on inhibitory interneurons [39–41]. Although neural plasticity in adults is more restricted, the underlying activity-dependent processes likely follow similar principles.

Molecular mechanisms of activity-dependent synaptic plasticity

Activity-dependent synaptic plasticity is conventionally discussed under the headings of long-term potentiation (LTP) and long-term depression (LTD). But LTP/LTD are deceptively simple terms encompassing a wide range of molecular processes [42,43]. The early phase of LTP (E-LTP) is triggered by Ca2+ influx linked to post-synaptic depolarization, which sets in motion molecular cascades mediated by phosphorylation and dephosphorylation of regulatory molecules (e.g. protein kinase C (PKC) and Ca2+-calmodulin-dependent protein kinase (CamKII)) that govern neurotransmitter receptor trafficking. E-LTP lasts 1–3 hours and is independent of gene expression. The late phase of LTP (L-LTP) begins with the transcription of immediate early genes (IEGs; e.g. Arc, Zif268) that control translational processes, which lead, on a time scale of hours, to structural changes in dendritic spines [44–46]. Thus, whereas electrophysiological event-related responses may last up to a few hundred milliseconds and BOLD hemodynamic responses typically evolve over ~16–20 s, the metabolic traces of the evoked activity persist over much longer time scales. These traces may underlie the observation that fMRI responses to task A are modulated by having performed unrelated task B during the past half hour [47].

The Hebbian principle (‘fire together → wire together’) is often invoked to account for resting state functional connectivity [48,49]. The mechanism underlying Hebbian learning, that is, spike-timing dependent synaptic plasticity (STDP), has been elucidated in considerable detail [50,51]. In brief, neural back-propagation of depolarization induced by a first excitatory stimulus removes the Mg2+ block at NMDA receptors, thereby allowing a second stimulus (if it occurs within a 20–85 ms window) to induce local Ca2+ entry, which initiates the LTP molecular cascade, ultimately reinforcing the association between the paired stimuli. Hebbian mechanisms undoubtedly play a central role in adult learning. Accordingly, it is reasonable to posit that synchronous spontaneous BOLD fluctuations that give rise to RSFC are due to a history of prior co-activation. However, a system dominated by unopposed Hebbian plasticity inevitably becomes either infinitely active or silent.
In contrast to Hebbian plasticity, which adjusts synaptic weights in the same direction as an applied stimulus, the brain also employs various mechanisms of homeostatic plasticity, which adjusts synaptic strengths in the opposite direction to return excitatory/inhibitory (E/I) balance and mean firing rate to prior set points [52]. Homeostatic plasticity includes cell-autonomous mechanisms that directly adjust neuronal excitability to counteract environmental stimuli, as well as multiplicative synaptic scaling, which preserves relative strengths between neighboring synapses, thereby maintaining currently represented information [53]. These homeostatic mechanisms operate at the level of dendritic branches [45], individual neurons [53], and large-scale circuits [54], and are active over multiple time scales [55,56]. A correlate of these homeostatic processes is ongoing turnover of synaptic proteins and lipids with half-lives on the order of ‘minutes, hours, days, weeks’ [57]. Modeling experiments suggest that homeostatic regulation of E/I balance plays a crucial role in maintaining the characteristic features of spontaneous brain activity [58]. Importantly, synaptic homeostasis is inseparable from consolidation, the process whereby brief changes in neural activity ultimately lead to stable memory [59,60]. Thus, it is reasonable to posit that spontaneous activity includes both Hebbian and homeostatic signaling.

**On-line versus off-line processes in electrophysiology**

Consolidation characteristically takes place after the events and associated behavioral responses that will later be remembered. This defining feature motivates the distinction between on-line versus off-line processes. The consolidation of episodic memory through parahippocampal place-cell replay in association with hippocampal sharp-wave ripples (SWR), especially during SWS, exemplifies off-line processing [61,62]. Consolidation of procedural memory appears to be less dependent on SWS, but nevertheless is said to take place off-line [63,64]. In contrast, perception, motor behavior, retrospection, prospection, and rumination, all exemplify on-line processes. It is the central thesis of the present work that the distinction between on-line versus off-line processing in the brain is logically parallel to the state alternation principle discussed above in connection with theoretical and artificial learning machines. Thus, by analogy, we suggest that particular regions of the brain exist, at any given time, in a state dominated by either on-line or off-line processes.

Honey et al. have recently pointed out that the brain switches between externally oriented versus internally oriented modes at multiple temporal and spatial scales [65]. This nomenclature differs from that used in the preceding discussion but we suggest that the distinction between external versus internal modes is closely related to, if not identical to, the distinction between on-line versus off-line processes. As noted above, wake versus sleep represents this distinction at the coarsest temporal and spatial scale. But neither wake nor sleep are homogeneous states. It is generally well recognized that sleep includes graded depth SWS as well as rapid eye movement (REM) stages. It probably is less well recognized that nominally awake subjects continually fluctuate between more versus less aroused states. In humans, this fluctuation manifests as variable task performance, changing EEG rhythms, and differing activity patterns as imaged with BOLD fMRI [19,66,67]. Similarly, awake rodents alternate between theta states, during which they actively explore their environment, versus quieter states during which theta is suppressed and SWRs occur [68–70]. In awake rodents, entorhinal cortex alternates between encoding versus retrieval modes depending on the phase of the theta rhythm [71]. Taking these considerations into account suggests that some portion of ongoing brain activity can be understood in terms of the two-phase learning machine principle manifesting as multiple, superimposed processes.

According to this model, each part of the brain alternates between on-line versus off-line states, and both states may be simultaneously present in different parts of the brain. Empirical evidence suggests that instantiation of the on-line state suppresses off-line activity locally. In the electrophysiology literature, this principle is known as stimulus quenching [72]. Probably the most robust illustration of stimulus quenching in fMRI is suppression of ongoing visual cortex BOLD signal fluctuations by eye opening [11,73]. It appears likely that ‘BOLD fluctuation quenching’ occurs in all parts of the cerebral cortex recruited by any task, although the magnitude of the effect may be modest [74]. BOLD fluctuation quenching is relevant to the observation that task performance modifies RS-FC (see below).

**Interpreting spontaneous BOLD fluctuations**

It is well-established that evoked BOLD responses are linked to event-related neural activity [75,76]. The physiological links between resting state neural activity and BOLD signal fluctuations have been relatively less well studied [77,78], but the available evidence suggests that stimulus-evoked responses and spontaneous fluctuations in LFP amplitude are similarly coupled to BOLD signals [79,80]. A separate line of investigation suggests that infra-slow (<0.1 Hz) EEG potentials directly mirror resting state BOLD fMRI signal fluctuations [81,82]. Conceivably, metabotropic glutamatergic signaling may also be linked to BOLD fMRI fluctuations, especially as metabotropic glutamate receptors are thought to play an important role in neural homeostasis [83], although, as far as we are aware, direct evidence supporting such a link has not been reported.

What fraction of resting state BOLD fMRI signal fluctuations represents on-line versus off-line processes? Precise
separation of these processes in humans is experimentally challenging and further confounded by artifact and other non-neural sources of variance in BOLD imaging \[84,85\]. However, numerous investigations of functional connectivity at rest and in various task states have provided significant insight. In general, it has been found that functional connectivity exhibits similar overall architecture regardless of state \[14,15,86\], albeit with specific measurable differences depending on task. Some investigators emphasize this latter observation, noting that it is possible to differentiate task states using FC \[9,87\]. Although this is true, Gratton et al. have shown that the effect of task state on FC is quantitatively minor in comparison to individual-specific and common group patterns of FC \[16\]. One might expect that an externally imposed task would have a substantially greater impact on functional connectivity than concurrent task-independent thought. Therefore, these results suggest that functional connectivity differences between subjects likely do not represent task-independent cognition. Moreover, to the extent that there is task-related FC modulation, some portion may be explained by spatially specific suppression of off-line activity in brain areas recruited by the task, as previously discussed \[74\]. By contrast, task-evoked BOLD signals exhibit high dependence on task demands with similar patterns of recruitment across subjects \[16\]. These findings support the notion that spontaneous and evoked BOLD signals likely reflect different underlying types of brain activity (i.e. off-line versus on-line).

This perspective is supported by a substantial literature on the effects of intensive task training on functional connectivity. This literature is premised on the idea that changes in functional connectivity reflect practice-related effects of Hebbian neural plasticity. Functional connectivity changes have been observed in the context of numerous training paradigms including visuomotor adaptation \[88,89\], Braille training in sighted individuals \[90\] visual perception practice \[91\], playing the Space Fortress videogame \[92\], and acquisition of episodic memory \[93\], among others \[94\].

Most recently, our laboratory has reported an experiment in which healthy participants had their dominant arm casted for two weeks \[95\]. Extended resting state fNIRI was acquired daily over the two weeks before, during, and after casting. This manipulation generated the largest within-subject RSFC changes of which we are aware. Specifically, motor cortex homotopic functional connectivity, which normally has a Pearson correlation \(-0.7\)–\(-0.8\), was dramatically reduced (by as much as \(-0.86\)) within a few days of casting. The effect presumably reflects plasticity induced by the motor accommodations enforced by the cast, for example, having to use the non-dominant limb for habitual activities of daily living. Crucially, comparable RSFC changes were not induced by wearing the cast only during scanning. The implication is that the RSFC effect depends on having had the cast on during the past several hours to days. The time scale of this effect, that is, hours to days, strongly suggests that the mechanisms underlying the observed alterations in spontaneous activity are related to homeostatic and consolidative mechanisms as opposed to instantaneous cognitive content. As previously discussed, synaptic plasticity involves a multi-stage molecular cascade comprising 2nd messenger signaling, gene transcription, and protein synthesis, which are expected to operate over a similar timescale.

In addition to large magnitude RSFC changes, casting led to increased amplitude of spontaneous fluctuations (ALFF) in the area undergoing plasticity and the emergence of spontaneous, large amplitude BOLD signal ‘pulses’. The latter unexpected phenomenon may be a consequence of focal motor cortex disinhibition giving rise to paroxysmal activity \[96\]. By analogy with SWRs, these pulses may reflect a state of elevated neural plasticity induced by the extreme experimental manipulation \[95,97\]. Importantly, the relative speed and magnitude of the casting effect suggests that RSFC can reflect recent experience to an extent greater than previously thought. The timecourse of the casting effect shows that it is possible to dramatically change RSFC in a matter of days, provided that the required adaptation to circumstances is of a sufficiently great magnitude. The anatomical specificity of the casting effect reflects the specificity of the behavioral constraint, which affected only the dominant upper extremity, but not the leg, face, or other functions involving activities of daily life. It should be emphasized that RSFC architecture normally is remarkably stable over short and long time-scales \[11,16,18\]. Indeed, the spatial specificity of the casting effect demonstrates that the correlation structure of spontaneous BOLD signal fluctuations is largely preserved, even as regions affected by the manipulation exhibit change. Thus, spontaneous BOLD activity may reflect the results of long-term Hebbian-based functional organization, but may also reflect processes associated with neural plasticity itself.

**Future directions**

Although the present arguments are circumstantial with regard to the physiological significance of spontaneous BOLD fluctuations, they are intended to provide a compelling framework for interpreting functional connectivity. Studies of RSFC, the effects of prior practice on RSFC, and the effects of concurrent task performance on functional connectivity may be most productively viewed from the perspective of overlapping on-line and off-line brain activity. In particular, manipulations of off-line activity (e.g. arousal, accumulated training effects, sensory deprivation, etc.) may be expected to impact FC at least as much as manipulations of cognitive content (though both may be expected to have a limited impact on an overall stable RSFC architecture). Substantial future work remains to validate this hypothesis and open
questions remain. For instance, how does the time course of changes in BOLD fluctuations relate to structural, vascular, and metabolic manifestations of brain plasticity? Advanced concurrent imaging techniques, for example, qBOLD, DTI, VASO (see Ref. [94] for review) in the context of experiments inducing plasticity would provide significant insight along these lines. For example, measures of metabolic demand, for example, glycolytic index as measured by PET [98] and BOLD signal fluctuation amplitude [99] should be concurrently enhanced in areas undergoing plasticity. Further, animal models that connect BOLD signals with direct genetic or optogenetic manipulations of molecular mechanisms of synaptic modulation may close the loop on the causal relation between these measures. Thus, we may find that spontaneous brain activity indexed by ongoing BOLD fluctuations is more closely aligned with mechanisms of plasticity and synaptic homeostasis than ongoing cognitive content.

**Author contributions**

TOL and AZS conceived and wrote the manuscript.

**Funding**

This work was supported by N.I.H. grants including MH112473 (TOL), NS080675 and NS098577 (AZS).

**Conflict of interest statement**

Nothing declared.

**Acknowledgements**

We thank Jennifer Enright, Evan Gordon, and the editor for helpful feedback on prior versions of the manuscript.

**References and recommended reading**

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest

1. Gloor P: Hans Berger on the electroencephalogram of man. The fourteen original reports on the human electroencephalogram. Electroencephalogr Clin Neurophysiol 1969, Suppl. 28:1-350.

2. Raichle ME: The resting brain: how intrinsic activity organizes brain function. Philos Trans R Soc Lond B Biol Sci 2015, 370.

3. Weisskoff RM et al.: Power spectrum analysis of functionally-weighted MR data: what’s in the noise? Proc ISMRM 1993, 1:7.

4. Triantafylloiu C et al.: Comparison of physiological noise at 1.5T, 3T and 7T and optimization of fMRI acquisition parameters. Neuroimage 2005, 26:243-250.

5. Fox MD et al.: The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A 2005, 102:9673-9678.

6. Power JD et al.: Functional network organization of the human brain. Neuron 2011, 72:665-678.

7. Biswal B et al.: Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 1995, 34:537-541.

8. Posner MI, Raichle ME: Images of Mind. Scientific American Library/Scientific American Books; 1994.

9. Gonzalez Castillo J et al.: Tracking ongoing cognition in individuals using brief, whole-brain functional connectivity patterns. Proc Natl Acad Sci U S A 2015, 112:8762-8767.

10. Lurie DJ et al.: Questions and controversies in the study of time-varying functional connectivity in resting fMRI. Neutr Neurosci 2020, 4:30-69.

11. Laumann TO et al.: On the stability of BOLD fMRI correlations. Cereb Cortex 2017, 27:4719-4732.

12. Samann PG et al.: Development of the brain’s default mode network from wakefulness to slow wave sleep. Cereb Cortex 2011, 21:2082-2093.

13. Mhuireachtaigh RN et al.: Cortical and subcortical connectivity changes during decreasing levels of consciousness in humans: a functional magnetic resonance imaging study using propofol. J Neurosci 2010, 30:9095-9102.

14. Cole MW et al.: Intrinsic and task-evoked network architectures of the human brain. Neuron 2014, 83:238-251.

15. Krienen FM, Yeo BT, Buckner RL: Reconfigurable task-dependent functional coupling modes cluster around a core functional architecture. Philos Trans R Soc Lond Ser B Biol Sci 2014, 369.

16. Gratton C et al.: Functional brain networks are dominated by stable group and individual factors, not cognitive or daily variation. Neuron 2018, 98:439-452 e5.

This paper analyzes a highly sampled dataset, the Midnight Scan Club (MSC), to formally quantify variability in functional connectivity accounted for by subject, task state, and session. The authors found that the bulk of variance in functional connectivity is attributable to common and individual-specific network features as opposed to task or session-specific features. These results suggest that spontaneous BOLD activity is largely not explained by ongoing cognition.

17. Laumann TO et al.: Functional system and aural organization of a highly sampled individual human brain. Neuron 2015, 87:657-670.

18. Poldrack RA et al.: Long-term neural and physiological phenotyping of a single human. Nat Commun 2015, 6:8885.

19. Shine JM et al.: The dynamics of functional brain networks: integrated network states during cognitive task performance. Neuron 2016, 92:544-554.

20. Power JD et al.: Characteristics of respiratory measures in young adults scanned at rest, including systematic changes and "missed" deep breaths. Neuroimage 2020, 204:116234.

21. Raichle ME, Mintun MA: Brain work and brain imaging. Annu Rev Neurosci 2006, 29:449-476.

22. Miall RC, Robertson EM: Functional imaging: is the resting brain resting? Curr Biol 2006, 16:R988-R1000.

Prescient, explicit articulation of the hypothesis that resting state brain activity reflects, at least in part, off-line processes underlying memory consolidation. The primary observations concern consolidation of procedural memory but apply as well to all forms of memory.

23. Vincent JL: Learning and memory: while you rest, your brain keeps working. Curr Biol 2009, 19:R484-6.

24. Marr D: A theory for cerebral neocortex. Proc R Soc Lond B Biol Sci 1970, 176:161-234.

25. Ackley DA, Hinton GE, Sejnowski TJ: A learning algorithm for boltzmann machines. Cogn Sci 1985, 9:147-169.

26. Hinton GE et al.: The "wake-sleep" algorithm for unsupervised neural networks. Science 1995, 268:1188-1191.

Hinton et al. provide an exceptionally clear description of an unsupervised algorithm that learns to classify inputs, for example, hand-written digits. The algorithm includes three layers and alternates between 'bottom-up' and 'top-down' phases. The authors employ several functionally equivalent terms in describing these two phases. Thus, 'bottom-up' ≈ 'recognition' (evaluation of classification error relative to inputs), 'top-down' ≈ generative (weight adaptation) ≈ 'sleep'.

27. Rumelhart D, Hinton G, Williams R: Learning representations by back-propagating errors. Nature 1986, 323:533-536.
Brain activity is not only for thinking Laumann and Snyder 135

28. Cirelli C, Tononi G: Is sleep essential? PLoS Biol 2008, 6:e216.

29. McNaughton BL et al.: Off-line reprocessing of recent memory and its role in memory consolidation: a progress report. In Sleep and Brain Plasticity. Edited by Maquet P, Smith C, Stickgold R. Scholarship Online; 2009.

30. Sejnowski TJ, Destexhe A: Why do we sleep? Brain Res 2000, 888:209-223.

31. Buzsáki G: Two-stage model of memory trace formation: a role for "noisy" brain states. Neuroscience 1989, 31:551-570. This classic paper includes an early account of how hippocampal sharp waves lead to Hebbian plasticity within the hippocampus by inducing long-term plasticity (LTP). This paper also describes the distinction between theta (exploratory) versus consummatory (non-exploratory) states in awake rodents.

32. Takesian AE, Hensch TK: Balancing plasticity/stability across brain development. Prog Brain Res 2013, 207:3-34.

33. Molnar Z, Luhmann HJ, Kanold PO: Transient cortical circuits match spontaneous and sensor-driven activity during development. Science 2020, 370.

34. Kirkby LA et al.: A role for correlated spontaneous activity in the assembly of neural circuits. Neuron 2013, 80:1129-1144.

35. Ackman JB, Crair MC: Role of emergent neural activity in visual map development. Curr Opin Neurobiol 2014, 24:166-175.

36. Winnubst J et al.: Spontaneous activity drives local synaptic plasticity in vivo. Neuron 2015, 87:399-410.

37. Byrne L, Sporns O, Smith LB: Developmental process emerges from extended brain-body-behavior networks. Trends Cogn Sci 2014, 18:395-403.

38. Hubel DH, Wiesel TN: Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. J Physiol 1962, 160:106-154.

39. Sur M et al.: Mechanisms of plasticity in the developing and adult visual cortex. Prog Brain Res 2013, 207:243-254.

40. Donato F, Rompani SB, Caroni P: Parvalbumin-expressing basket-cell network plasticity induced by experience regulates adult learning. Nature 2013, 504:272-276.

41. Kullmann DM et al.: Plasticity of inhibition. Neuron 2012, 75:951-962.

42. Bear MF, Malenka RC: Synaptic plasticity: LTP and LTD. Curr Opin Neurobiol 1994, 4:389-399.

43. Baltaci SB, Mogulkoc R, Baltaci AK: Molecular mechanisms of early and late LTP. Neurochem Res 2019, 44:281-296.

44. Baudry M et al.: Multiple cellular cascades participate in long-term potentiation and in hippocampus-dependent learning. Brain Res 2015, 1621:73-81.

45. Govindarajan A et al.: The dendritic branch is the preferred integrative unit for protein synthesis-dependent LTP. Neuron 2011, 69:132-146.

46. Xu T et al.: Rapid formation and selective stabilization of synapses for enduring motor memories. Nature 2009, 462:915-919.

47. Peigneux P et al.: Offline persistence of memory-related cerebral activity during active wakefulness. PLoS Biol 2006, 4:e100.

48. Dosenbach NU et al.: Distinct brain networks for adaptive and stable task control in humans. Proc Natl Acad Sci U S A 2007, 104:11073-11078.

49. Guerra-Carrillo B, Mackey AP, Bunge SA: Resting-state fMRI: a window into human brain plasticity. Neuroscientist 2014, 20:522-533.

50. Markram H et al.: Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. Science 1997, 275:213-215.

51. Bi G, Poo M: Synaptic modification by correlated activity: Hebb's postulate revisited. Annu Rev Neurosci 2001, 24:139-166.

52. Kavalali ET, Monteggia LM: Targeting homeostatic synaptic plasticity for treatment of mood disorders. Neuron 2020, 106:715-726.

53. Turrigiano GG, Nelson SB: Homeostatic plasticity in the developing nervous system. Nat Rev Neurosci 2004, 5:97-107. This review paper explains why homeostatic mechanisms, for example, synaptic scaling and regulation of excitatory/inhibitory (E/I) balance, are needed to stabilize neural systems that undergo Hebbian plasticity. The paper outlines distinct roles for AMPA and NMDA receptors in LTP/LTD. The emphasis is on homeostasis during development but the fundamental principles apply as well to adult learning.

54. Turrigiano G: Homeostatic synaptic plasticity: local and global mechanisms for stabilizing neuronal function. Cold Spring Harb Perspect Biol 2012, 4:a005736.

55. Zerfke F, Gerstner W, Ganguli S: The temporal paradox of Hebbian learning and homeostatic plasticity. Curr Opin Neurobiol 2017, 43:166-176.

56. Bittner KC et al.: Behavioral time scale synaptic plasticity underlies CA1 place fields. Science 2017, 357:1033-1036.

57. Marder E, Goaillard JM: Variability, compensation and homeostasis in neuron and network function. Nat Rev Neurosci 2006, 7:563-574.

58. Heiliger PJ et al.: Local inhibitory plasticity tunes macroscopic brain dynamics and allows the emergence of functional brain networks. Neuroimage 2016, 124:85-95.

59. Abbott LF, Nelson SB: Synaptic plasticity: taming the beast. Nat Neurosci 2000, 3 Suppl:1178-1183.

60. Axmacher N et al.: Memory processes during sleep: beyond the standard consolidation theory. Curr Opin Neurobiol 2017, 43:166-176.

61. Bittner KC et al.: Behavioral time scale synaptic plasticity underlies CA1 place fields. Science 2017, 357:1033-1036.

62. Marder E, Goaillard JM: Variability, compensation and homeostasis in neuron and network function. Nat Rev Neurosci 2006, 7:563-574.

63. Heiliger PJ et al.: Local inhibitory plasticity tunes macroscopic brain dynamics and allows the emergence of functional brain networks. Neuroimage 2016, 124:85-95.

64. Abbott LF, Nelson SB: Synaptic plasticity: taming the beast. Nat Neurosci 2000, 3 Suppl:1178-1183.

65. Axmacher N et al.: Memory processes during sleep: beyond the standard consolidation theory. Cell Mol Life Sci 2009, 66:2285-2297.

This review paper explains why the formation of episodic memory requires alternation between an encoding phase (wake; online) versus a consolidation phase (sleep; offline). Each phase is associated with distinct patterns of information flow between the cerebral cortex and the hippocampus (the “hippocampal-cortical dialog”, cf Buzsáki, Cerebral Cortex, 1990). The authors also contrast episodic versus procedural (motor) memory as well as SWS versus REM sleep.

66. Buzsáki G: Hippocampal sharp wave-ripple: a cognitive biomarker for episodic memory and planning. Hippocampus 2015, 25:1073-1188.

67. Vyazovskiy VV, Harris KD: Sleep and the single neuron: the role of global slow oscillations in individual cell rest. Nat Rev Neurosci 2013, 14:443-451.

68. Dayan E, Cohen LG: Neuroplasticity subserving motor skill learning. Neuron 2011, 72:443-454.

69. Robertson EM, Press DZ, Pascual-Leone A: Off-line learning and the primary motor cortex. J Neurosci 2005, 25:6372-6378.

70. Honey CJ, Newman EL, Scharpio AC: Switching between internal and external modes: a multiscale learning principle. Neur Netw 2018, 1:339-356.

Honey et al. argue that the brain continually switches between externally biased (online in our nomenclature) versus internally biased (offline in our brain activity).
nomenclature) modes at multiple spatial and temporal scales. According to this perspective, sleep versus wake represents the broadest temporal scale of mode switching. The implication is that multiple processes are simultaneously present in the brain within which online versus offline states alternate.

66. Sadagiani S et al.: Intrinsic connectivity networks, alpha oscillations, and tonic alertness: a simultaneous electroencephalographyfunctional magnetic resonance imaging study. J Neurosci 2010, 30:10243-10250.

67. Kucyi A et al.: Dynamic brain network correlates of spontaneous fluctuations in attention. Cereb Cortex 2017, 27:1831-1840.

68. van de Ven GM et al.: Hippocampal offline reactivation consolidates recently formed cell assembly patterns during sharp wave-ripples. Neuron 2016, 92:968-974.

69. Buzsaki G: Theta oscillations in the hippocampus. Neuron 2002, 33:325-340.

70. Vaz AP et al.: Coupled ripple oscillations between the medial temporal lobe and neocortex retrieve human memory. Science 2019, 363:975-978.

71. Hasselmo ME: The role of acetylcholine in learning and memory. Curr Opin Neurobiol 2006, 16:710-715.

72. Churchland MM et al.: Stimulus onset quenches neural variability: a widespread cortical phenomenon. Nat Neurosci 2010, 13:369-378.

73. Bianciardi M et al.: Modulation of spontaneous fMRI activity in human visual cortex by behavioral state. Neuroimage 2009, 45:160-168.

74. He BJ: Spontaneous and task-evoked brain activity negatively interact. J Neurosci 2013, 33:4672-4682.

75. Kim SG, Ogawa S: Biophysical and physiological origins of blood oxygenation level-dependent fMRI signals. J Cereb Blood Flow Metab 2012, 32:1188-1206.

76. Logothetis NK et al.: Neuropsychological investigation of the basis of the fMRI signal. Nature 2001, 412:150-157.

77. Leopold DA, Maier A: Ongoing physiological processes in the cerebral cortex. Neuroimage 2012, 62:2190-2200.

78. Scholvinck ML et al.: Neural basis of global resting-state fMRI activity. Proc Natl Acad Sci U S A 2010, 107:10238-10243.

79. Bruyns-Haylett M et al.: The resting-state neurovascular coupling relationship: rapid changes in spontaneous neural activity in the somatosensory cortex are associated with haemodynamic fluctuations that resemble stimulus-evoked haemodynamics. Eur J Neurosci 2013, 38:2902-2918.

80. Shmuel A, Leopold DA: Neuronal correlates of spontaneous fluctuations in fMRI signals in monkey visual cortex: Implications for functional connectivity at rest. Hum Brain Mapp 2008, 29:751-761.

81. Hiltunen T et al.: Infra-slow EEG fluctuations are correlated with resting-state network dynamics in fMRI. J Neurosci 2014, 34:356-362.

82. Pan WJ et al.: Infra-slow LFP correlates to resting-state fMRI BOLD signals. Neuroimage 2013, 74:288-297.

83. Kavalali ET: The mechanisms and functions of spontaneous neurotransmitter release. Nat Rev Neurosci 2015, 16:5-16.

84. Power JD et al.: Methods to detect, characterize, and remove motion artifact in resting state fMRI. Neuroimage 2014, 84:320-341.

85. Power JD et al.: Sources and implications of whole-brain fMRI signals in humans. Neuroimage 2017, 146:609-625.

86. Gratton C et al.: Evidence for two independent factors that modify brain networks to meet task goals. Cell Rep 2016, 17:1276-1288.

87. Shirer WR et al.: Decoding subject-driven cognitive states with whole-brain connectivity patterns. Cereb Cortex 2012, 22:158-165.

88. Albert NB, Robertson EM, Miall RC: The resting human brain and motor learning. Curr Biol 2009, 19:1023-1027.

89. Shannon BJ et al.: Brain aerobic glycolysis and motor adaptation learning. Proc Natl Acad Sci U S A 2016, 113:E3782-91.

90. Siuda-Krzywicka K et al.: Massive cortical reorganization in sighted Braille readers. eLife 2016, 5:e10762.

91. Lewis CM et al.: Learning sculpts the spontaneous activity of the resting human brain. Proc Natl Acad Sci U S A 2009, 106:17558-17563.

92. Voss MW et al.: Effects of training strategies implemented in a complex videogame on functional connectivity of attentional networks. Neuroimage 2012, 59:138-148.

93. Tambini A, Ketzel N, Davachi L: Enhanced brain correlations during rest are related to memory for recent experiences. Neuron 2010, 65:280-290.

94. Tardif CL, Advanced MRI et al.: techniques to improve our understanding of experience-induced neuroplasticity. Neuroimage 2016, 131:55-72.

95. Newbold DJ et al.: Plasticity and spontaneous activity pulses in a disused human brain circuit. Neuron 2020, 107:580-589 e6. This paper reports on the effects of casting of the dominant arm on whole-brain RSFC. The authors observed dramatic changes in RSFC in motor cortex. Notably, this effect was only observed after having had the cast on for at least hours. They also observed the emergence of discrete large amplitude pulses in spontaneous BOLD activity not present before casting.

96. Rosenthal ZP et al.: Local perturbations of cortical excitability propagate differentially through large-scale functional networks. Cereb Cortex 2020, 30:3352-3369.

97. Fair DA, Yeo BTT: Precision neuroimaging opens a new chapter of neuroplasticity experimentation. Neuron 2020, 107:401-403.

98. Vaishnavi SN et al.: Regional aerobic glycolysis in the human brain. Proc Natl Acad Sci U S A 2010, 107:17757-17762.

99. Garrett DD et al.: The modulation of BOLD variability between cognitive states varies by age and processing speed. Cereb Cortex 2013, 23:684-693.

100. Mitra A et al.: Propagated infra-slow intrinsic brain activity reorganizes across wake and slow wave sleep. eLife 2015, 4.

101. Hutchison RM et al.: Resting-state networks show dynamic functional connectivity in awake humans and anesthetized macaques. Hum Brain Mapp 2013, 34:2154-2177.

102. Palanca BJ et al.: Resting-state functional magnetic resonance imaging correlates of sevoflurane-induced unconsciousness. Anesthesiology 2015, 123:346-356.

103. Gordon EM et al.: Precision functional mapping of individual human brains. Neuron 2017, 95:791-837 e7.

104. Damoiseaux JS et al.: Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci U S A 2006, 103:13848-13853.

105. Biswal BB et al.: Toward discovery science of human brain function. Proc Natl Acad Sci U S A 2010, 107:4734-4739.

106. Vincent JL et al.: Intrinsinc functional architecture in the anaesthetized monkey brain. Nature 2007, 447:83-86.

107. Hutchison RM et al.: Functional networks in the anesthetized rat brain revealed by independent component analysis of resting-state fMRI. J Neurophysiol 2010, 103:3398-3406.

108. Mantini D et al.: Default mode of brain function in monkeys. J Neurosci 2011, 31:12964-12962.