

Functional interactions between intrinsic brain activity and behavior

Sepideh Sadaghiani^{a,*}, Andreas Kleinschmidt^b

^a Hellen Wills Neuroscience Institute, University of California Berkeley, Berkeley, CA 94720, USA

^b Department of Clinical Neurosciences, University Hospital (HUG) and University of Geneva, CH-1211 Geneva, Switzerland

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ABSTRACT

The brain continuously maintains a remarkably high level of intrinsic activity. This activity is non-stationary and its dynamics reveal highly structured patterns across several spatial scales, from fine-grained functional architecture in sensory cortices to large-scale networks. The mechanistic function of this activity is only poorly understood. The central goal of the current review is to provide an integrated summary of recent studies on structure, dynamics and behavioral consequences of spontaneous brain activity. In light of these empirical observations we propose that the structure of ongoing activity and its itinerant nature can be understood as an indispensable memory system modeling the statistical structure of the world. We review the dynamic properties of ongoing activity, and how they are malleable over short to long temporal scales that permit adapting over a range of short- to long-term cognitive challenges. We conclude by reviewing how the functional significance of ongoing activity manifests in its impact on human action, perception, and higher cognitive function.

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Introduction

The brain is often compared to a computer or related metaphors. But unlike man-made computers that are highly modular the brains themselves that designed such computers have a very different layout. In the brain, the counterparts of a central processor, the software and the data memory seem to be housed in one and the same entity. This entity is the brain's wiring structure or “connectome”, a structure that is continuously modified by memory traces from development and experience. Radically different from computers, operational memory encoded by the connectivity structure is permanently at least partially replayed even in the absence of extrinsically induced processing demands. This process underpins the observation of “spontaneous” or intrinsic activity. Moment-to-moment fluctuations of intrinsic activity hence reflect the past history of the system but they also influence present and future operations. Current operations in turn again leave traces and thereby shape the connectivity pattern. In the following, we elaborate on this condensed sketch in more detail.

First, we discuss this two-way relation between intrinsic brain activity and operations underlying perception and behavior. The material reviewed speaks to this interaction as an essential feature of the brain's processing architecture rather than an epiphenomenon of neurophysiological mechanisms. It further suggests that to adequately understand brain function one needs to deepen the empirical study of intrinsic neural activity and conceptually incorporate these results into functional models.

Throughout this review, we discuss relevant research from the perspective of what it tells us about the functional role of spontaneous brain activity. In the first section, we describe how the structure of ongoing activity reflects a memory system modeling the statistical structure of the world. We then discuss why brain function requires such an internal model, and finally propose reasons for why this model operates in an itinerant fashion. The second section characterizes more closely the dynamic structure of ongoing activity. We discuss how this structure is malleable over short to long temporal scales permitting to adapt to cognitive challenges ranging from current perception to gradual learning. The last section describes how, as a consequence, itinerant ongoing activity fluctuations affect human perception and behavior.

The brain's internal memory of external causal dynamics

Functional importance of ongoing brain activity is suggested by its continuous presence and its sheer amount on top of which evoked brain responses appear as minor perturbations. Ongoing activity hence accounts for the bulk of brain energy consumption, which in turn constitutes 1/5 of total body energy expenditure (Raichle, 2009). The most striking property of intrinsic activity is that it fluctuates spontaneously. Over several orders of magnitude across both time and space these fluctuations are highly structured (for a discussion on temporal and spatial characteristics see Sadaghiani et al., 2010). We propose that this spatiotemporal structure of ongoing activity is a way of replaying intrinsic, operational network memory. Here, we use the term memory to refer to the sum of the system's evolved connections, recent activity history, and current context that are reflected

* Corresponding author.

E-mail address: sepideh.sadaghiani@gmail.com (S. Sadaghiani).

in dynamic network states. The notion of memory thus encompasses structural network connectivity (Fuster, 1997), functional connectivity continuously expressed on the structural connectivity backbone (Lewis et al., 2009), and context-sensitive dynamics of these ongoing activity patterns (Fontanini and Katz, 2008; Stopfer and Laurent, 1999). We thereby integrate several perspectives on memory. This means that our usage of the term extends beyond the usual cognitive notion of what memory is.

Orientation preference maps of primary visual cortex provide an intuitively accessible illustration of network memory and of its continuous reactivation in a spatio-temporal activity structure. The spatially ordered organization of orientation columns directly reflects observable regularities of the world, specifically continuous edges and contours of particular orientations. This structural organization is expressed in functional connectivity through reactivation of and rapid switching between different iso-orientation domains (~40 ms per state, Kenet et al., 2003; cf. Fig. 1A). Importantly, these functional dynamics are continuous as demonstrated during anesthesia, i.e., mental states arguably lacking consciousness and perception. Although in principle present at birth (Wiesel and Hubel, 1974), this mesoscopic organization of structural (and by consequence functional) connectivity is highly dependent upon and shaped by visual experience over the course of early development. Cats raised in environments that lack certain spatial orientations will develop aberrant orientation preference maps and show deficient perceptual responses to stimuli of the respective orientation (Blakemore and Cooper, 1970; Blasdel et al., 1977). Notably, experience- and activity-dependent changes continue to shape these maps in the adult visual cortex (Dragoi et al., 2000; Godde et al., 2002).

Recurrent co-activation patterns also occur at larger spatio-temporal scales. At these scales they represent more complex levels of regularities in the environment, of our perceptions and actions in it, and of our internal “world”. At the mesoscopic level illustrated above, the spontaneous co-activation of corresponding orientation-selective neurons spans across segregated hypercolumns. Similarly, at macroscopic scales correlated activity occurs between neural populations in segregated but functionally related brain regions. At the larger scale of visual field maps

for example, activity in retinotopically corresponding neural populations of V1 and V3 fluctuates coherently, as recently observed in humans using fMRI in the absence of visual input (Heinzle et al., 2011; Fig. 1B). At the largest scale, spontaneous co-fluctuations emerge over distant, functionally connected brain regions giving rise to intrinsic connectivity networks (ICNs, also referred to as resting state networks; Figs. 1C–D).

These large-scale networks have received much attention in the recent neuroimaging literature – not least due to the slow neural activity modulations at this spatial scale that are particularly well captured by the low pass filter characteristics of hemodynamic signals (highest power below 0.1 Hz, Zarahn et al., 1997). Again, at least qualitatively, this intrinsic activity occurs across all mental states, including engaged states (Eckert et al., 2009; Fair et al., 2007) as well as in the absence of explicit cognitive task demands or even consciousness (Fransson, 2005; Greicius et al., 2003, 2008; Horowitz et al., 2007).

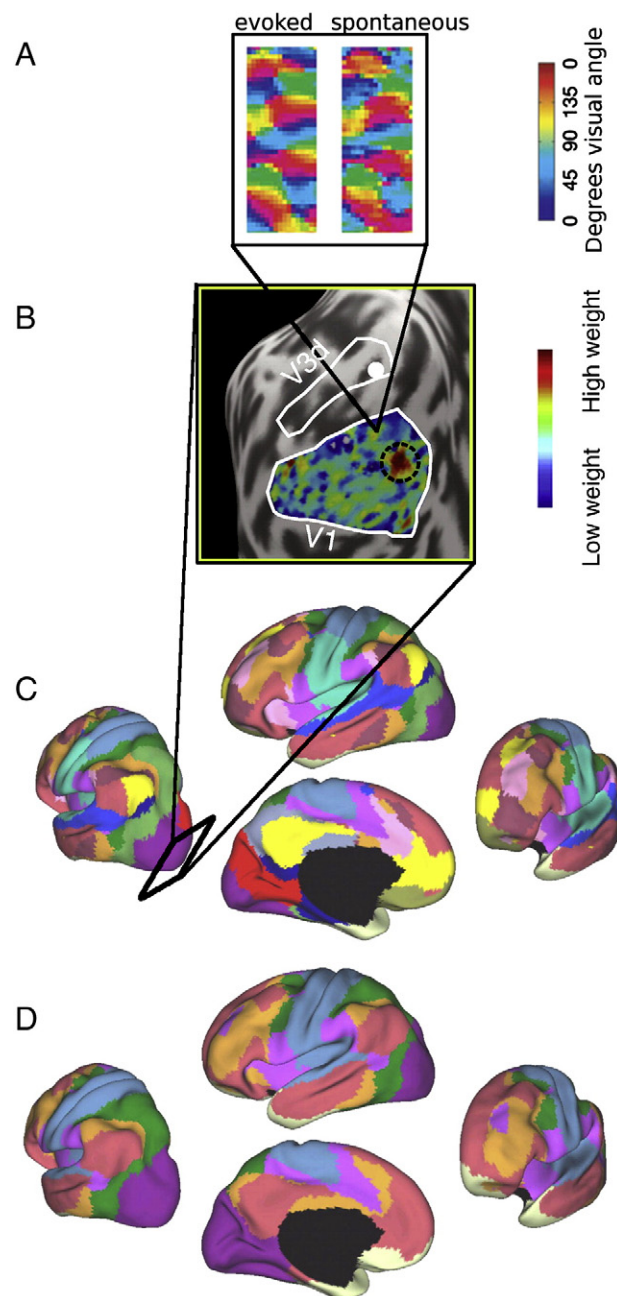


Fig. 1. Hierarchical spatio-temporal structure of ongoing brain activity. A) On a very fine spatial scale spontaneous activity in V1 displays highly structured spatio-temporal patterns that closely resemble those evoked by selective stimulus features, i.e. edges and contours of particular orientations (color coded according to visual angle). Ongoing activity is coherent across neural populations with a similar orientation preference, and switches iteratively between iso-orientation domains of the pinwheel maps. Optical imaging results from few mm² of cat V1 under anesthesia (modified from Kenet et al., 2003). B) On a larger spatial scale ongoing activity is spatio-temporally structured in retinotopic maps. The color code illustrates the predictive power of V1 voxels (distribution of weights of the optimal linear combination of signal time courses) to predict spontaneous activity fluctuations of the V3 voxel marked by a white dot. The V1 area of highest predictive power (dashed circle) corresponds to the same position in retinotopic space as the predicted V3 voxel. Functional MRI of human occipital cortex during resting wakefulness. Posterior view of the inflated occipital cortical surface (modified from Heinzle et al., 2011). C) At a yet larger spatial scale spontaneous activity delineates large subdivisions within visual cortices. These are driven by topographic eccentricity, however, on a very coarse scale of a central (purple) and a peripheral sub-system (bright red). Functionally connected regions include local sensory networks such as the visual subdivisions, but also distributed networks of association regions. Here, 17 intrinsic functional connectivity networks (ICNs, represented by different colors) are estimated. D) These local and distributed ICNs can be defined at different levels of the correlation hierarchy. This time, the brain is parceled into 7 ICNs, and several ICNs previously segregated in finer subdivisions in B) are now unified into larger ICNs at this coarser level of spatio-temporal organization. C–D) Human functional MRI during resting wakefulness. Surface-based views of the left hemisphere. Areas that show coherent activity fluctuations (functional connectivity) are marked by the same color (modified from Yeo et al., 2011). This figure illustrates that multiple spatial levels of functional connectivity are hierarchically embedded and concurrently present in the brain. Note that temporal scale might be tightly linked to spatial scale. While spontaneous iso-orientation domains switch in tens of milliseconds (A) large-scale networks observed with fMRI show activity fluctuations on the order of tens of seconds (C–D).

Similar to experience-dependent plasticity of functional architecture within visual areas, the connectivity memory of ICNs evolves through experience. Their rough connectivity structure forms during developmental maturation (Dosenbach et al., 2010; Smyser et al., 2011). Importantly, however, experience continuously shapes this matrix in more subtle ways throughout life. We consider this process to be the substrate of fine-tuning of the internal model to ever-changing environmental demands. In the next review section, we will discuss these adaptive dynamics of intrinsic activity patterns at the macroscopic scale on the basis of recent functional imaging findings.

These analogies across the range of spatio-temporal scales suggest a generic role for ongoing activity. The spatial structure of ongoing activity patterns shares features with patterns from neural ensembles that are co-activated during stimulation or task performance. It therefore seems as if ongoing activity recapitulates processes or internal contexts that are closely related to those evoked by tangible functional demands that arise during specific activation paradigms where specific neural operations are driven by sensory input, instructed by cognitive sets or result in actions. This holds true across spatio-temporal scales, from e.g. orientation preference maps of visual cortex (Tsodyks et al., 1999) to large-scale ICNs (Smith et al., 2009). In terms of specific neural processes, at the microscopic level, it has been observed that evoked population spiking patterns replay a subset of all possible spatio-temporal patterns iteratively occurring in spontaneous activity (Luczak et al., 2009). A close relation is also supported by the impact of ongoing activity fluctuations on subsequent perception and behavior. Very recently for instance, it has been shown that specific replay sequences over place cells predict future navigation (Pfeiffer and Foster, 2013). Ongoing activity levels in specialized sensory regions also influence perception by introducing a bias towards or against the respective preferred stimuli. Examples include an impact of ongoing activity levels in fusiform face area (FFA) on face perception (Hesselmann et al., 2008a), in motion-sensitive middle temporal region (MT+) on motion perception (Hesselmann et al., 2008b), and in early auditory cortex on auditory perception (Sadaghiani et al., 2009). An equivalent effect is observed for spontaneous behavioral variability in higher order cognitive functions such as cognitive and attentional control. This variability seems to be tied to fluctuations in ongoing activity of large-scale networks that are engaged by the higher order functions in task settings (Boly et al., 2007; Coste et al., 2011; Sadaghiani et al., 2009). The content-specific and context-sensitive fashion (Sadaghiani et al., 2009) in which ongoing activity impacts the respective behavioral processes hence supports the notion that this activity reflects at least in part processes akin to those observed during task. This issue is discussed in detail in the last section of this review.

We next seek to understand why the brain is based on a constantly active intrinsic memory system in spite of the large metabolic cost incurred. A functional exploration of this question may be most insightful, and formal frameworks may help to understand the role of intrinsic activity. Regarding perception, it has been pointed out that we operate (in the world) on the basis of sensory input that by itself is too sparse, noisy and ambiguous to be interpretable (Kersten et al., 2004; Lochmann and Deneve, 2011). In such a setting, sensory perception is an experience-dependent, learned capacity (Tsodyks and Gilbert, 2004). The ability to perceive and to continuously learn to perceive more precisely develops gradually and automatically over many repeated exposures to the respective stimuli. This ability is being engraved in an adaptive network connectivity structure (cf. e.g. orientation preference maps) that provides the basis for model-driven perceptual inference. We suggest that such an internal model is likely reflected in ongoing activity patterns (Hesselmann et al., 2010; Sadaghiani et al., 2010). Notably, it is not the mere structural connectivity but rather the current active synaptic circuitry or network state that provides the indispensable operational context at any given moment (Fontanini and Katz, 2008). The coherent intrinsic activity patterns are robust and only slightly influenced by external

input. Hence, sensory evoked neural activity likely represents the modulation of ongoing circuit dynamics by input signals, rather than directly reflecting the structure of the input signal itself (Fiser et al., 2004). In fact, as noted above, evoked neural responses are suggested to be drawn from a larger set of possible spatio-temporal patterns observed in spontaneous activity (Luczak et al., 2009). Ongoing activity patterns may hence be thought to reflect an internal model of causal dynamics in the world. The trajectory of this model corresponds to the individual's perceptual, behavioral and emotional experiences. An important clarification here is that only a small fraction of this activity is likely to be introspectively accessible. In other words, our consciousness of these processes is limited and consciousness is not required for maintaining this trajectory. At any time point on its trajectory this model generates varying, conscious or non-conscious predictions about the future. Put otherwise, different positions on the trajectory correspond to different and specific predictions. These predictions are relevant and useful for a hierarchical inference machinery that integrates prior information in form of non-random activity states with current extrinsic operations such as interpreting sensory input. However, this principle is not restricted to perceptual inference. For example, motor control can be viewed as fulfilling prior expectations about proprioceptive sensations (Friston et al., 2010). And motor learning is likewise reflected in the gradual incorporation and optimization of Bayesian priors (Körding and Wolpert, 2004). In the next section, we will discuss the emergence of motor learning as changes in the intrinsic functional connectivity structure. More generally, in the suggested view, the brain seeks to predict consequences of its actions. And this principle may well extend to higher cognitive behaviors such as reward-based decision-making (Friston, 2010). We propose that this process includes the incorporation of patterns of past experience in the form of ongoing activity fluctuations into moment-to-moment processing.

Importantly, ongoing activity dynamics also manifest in the absence of dynamic sensory information or behavioral demands. From a functional perspective, just because sensory inputs are not currently available the brain will not model the world as having stopped (Sadaghiani et al., 2010). While real environments are continuously changing and not fully transparent the brain maintains an active representation of their attributes. Although dynamic this representation can provide an informed computational context for current and potentially upcoming operations. Another reason for the continuous expression of spontaneous activity is the indispensable role of intrinsic replay of activity patterns for maintaining the biological substrate of network memory. The most prominent example is the optimization (consolidation) of synaptic connections during sleep (Diekelmann and Born, 2010; Vyazovskiy et al., 2008). However, network and memory consolidation is probably a prominent feature of ongoing activity during wake states as well (Foster and Wilson, 2006; Tambini et al., 2010). Indirect support for a strong role of coherent intrinsic activity in network consolidation comes from its reverse process, i.e. the degradation of functional connectivity patterns. Focal lesions to the brain cause functional changes beyond the damaged area including distant but functionally connected brain regions, a principle referred to as diaschisis (Gratton et al., 2012). And in various forms of degenerative brain disease neural connections that coherently fire together not only wire together but also die together (Seeley et al., 2009). This phenomenon is possibly due to the absence of reverberating activity for re-consolidation subsequent to a loss of neurons in the lesioned network node. The degree to which intrinsic activity patterns return towards normal values is associated with the rate of recovery of the related cognitive and behavioral functions (He et al., 2007).

Above, we have proposed that ongoing activity across different spatio-temporal scales may fulfill equivalent functions from a Bayesian point of view. We acknowledge, however, that electrophysiological, optical and functional imaging methods in the cited studies measure very different signals potentially reflecting different neural processes.

It therefore currently remains speculative whether spatiotemporal structure displayed in ongoing activity at a very fine spatial scale is caused by the same neural processes as structure on the level of the entire brain. We here suggest, however, that an intrinsic memory-based account of the brain may be well-suited to explain the function of spontaneous activity even across differing neural processes.

Another question concerns the fluctuating nature of intrinsic activity. At the mesoscopic neural level, intrinsic brain activity continuously switches between different competing and complimentary sensory attributes such as the aforementioned orientation preference states (Kenet et al., 2003) or spatial locations (Heinzle et al., 2011). At the macroscopic level and very low speed, intrinsic brain activity continuously wanders through distinct ICNs underlying different functions. It is this very feature of intrinsic activity that has permitted characterizing brain networks on the basis of functional connectivity measures; these measures describe the extent of itinerant activity (and not stationary activity levels) thus exploiting the most prominent characteristic of intrinsic functional networks. Ongoing activity fluctuations often have very high amplitudes that are easily in the same range as even strong evoked responses (Fox et al., 2006). Why is system memory held on-line in an itinerant rather than more stable or tonic manner?

Apart from possible biological limitations to sustained activity we again take a functional approach to this question. In a Bayesian view of the brain, intrinsic activity fluctuations correspond to the optimization or selection of competing internal models, using itinerant searches over different hypotheses (models) about the world. Unstructured fluctuations (or noise) in local ongoing activity are thought to be the driving force that ensures these itinerant transitions between different metastable neuronal network states (Deco et al., 2011; Ghosh et al., 2008). For example, ongoing activity dynamics in the spatio-temporal form of orientation maps have been successfully modeled as noise-driven transitions between multistable attractors of an intracortical network (Blumenfeld et al., 2006). Likewise, on the larger scale of ICNs, spontaneous activity fluctuations emerge as transitions between multistable network configurations on the backbone of a (relatively) stable anatomical skeleton (Deco et al., 2011). These network configurations include not only the ICNs most often “visited” by the brain, but also emerge and dissolve fluidly across other, less stable configurations. This dynamics is proposed to reflect the exploration of the array of cognitive architectures that the brain has available (Deco et al., 2013). In the context of a Bayesian view, these intrinsic activity fluctuations reflect the dynamic nature of the underlying internal model. This model does not remain locked in a stationary mode but stays malleable by continuously exploring hypotheses regarding future experience and action. Itinerant activity has proven fruitful in modeling perception (e.g., Kiebel et al., 2009) and planning (e.g., Namikawa and Tani, 2010). Supporting this approach, cortical activity has been formulated in terms of itinerant dynamics (e.g., Tsuda, 2001). Tsuda extends this model based on neurodynamic itinerancy to a neural theory of (paradoxically stable) episodic memory.

It is important to point out that the views expressed here are not at odds with other accounts of the role of ongoing activity. A more homeostatic metabolic take on ongoing activity for instance considers a “housekeeping” role for ongoing activity where these patterns mainly serve maintenance of synaptic circuits (Duyin, 2011; Marder and Goaillard, 2006) and network consolidation (discussed above). This view cannot be dissociated from the functional consequences it would have on cognitive processes. And conversely, it is hard to imagine how an internal model could be implemented in the brain and continuously tuned without recurring to modifications of synaptic circuitry. This link leads us to the next section where we review recent functional imaging literature regarding the encoding of experience and memory in terms of short-term and long-term changes of ongoing activity fluctuation patterns.

Experience shapes intrinsic brain activity

Long-term memory, including declarative memory (acquired by conscious effort or incidental to manipulation of items), and implicit memory in perceptual and motor systems, are relatively stable phenomena. Nonetheless, a large body of recent literature has investigated their formation in terms of changes to the inherently dynamic intrinsic activity fluctuations. Most of these studies apply a rest-task-rest design comparing functional connectivity before and after a training task of varying duration and nature. Lewis et al. (2009) investigated the effects of several days of intense training in a shape-identification task. They observed changes in intrinsic connectivity between visual areas and higher order frontal and parietal regions that presumably generate visuospatial top-down predictions as for instance expressed in the spatially selective allocation of attention. Another field of particularly extensive research has been the motor domain. Vahdat et al. (2011) used extensive sensorimotor training on a force-field robot arm to separately investigate perceptual and motor aspects of learning. They observed specific functional connectivity changes within motor, cerebellar and somatosensory cortices that were linearly related to individual rates of perceptual and motor improvement. Ma et al. (2011) observed an increase in resting state functional connectivity within motor-related areas accompanying four weeks of daily sequential finger movement training. The above studies of extensive learning in all likelihood involve structural connectivity changes that impact the observed functional connectivity changes. Taubert et al. (2010, 2011) concurrently investigated functional and structural connectivity plasticity at multiple time points along several sessions of whole-body balance training over 6 weeks. They observed functional connectivity increases that were accompanied by corresponding structural changes between supplementary motor cortex and the parietal lobe. Both, functional and structural measures changed with gradual improvement in motor performance.

However, plasticity of intrinsic functional connectivity also occurs at time scales too short to involve gross structural connectivity changes. A rapidly growing body of experiments has established dynamic short-term plasticity of intrinsic functional connectivity after task exposure typically in the range of only 10–20 min duration within the same MRI scanning session. Albert et al. (2009) observed increased functional connectivity strength in the fronto-parietal top-down control ICN and a cerebellar ICN after few minutes of motor learning. No changes occurred in the control group engaged in a movement task that did not require sensorimotor re-adjustments. This short-term plasticity has likewise been explored in cognitive learning. Tambini et al. (2010) selectively addressed functional connectivity between hippocampus and the relevant visual category-selective area after associative learning of picture pairs. They found increased functional connectivity between these regions immediately following the encoding task, the magnitude of which predicted differences in associative memory recall across participants after the scanning session. As noted in the previous section, these results speak to a role of replay as observed in ongoing activity patterns in the consolidation of memory into structural changes. In other words, anatomical connectivity is shaped by plasticity of functional connectivity. Functional connectivity in turn is highly dynamic rather than being an emergent property of uncorrelated noise played out on a structural skeleton. Completing the analogy, the vertebrate skeleton is likewise a slave to soft tissue. It provides a defining backbone to the musculature, yet repeated dynamic state changes from postures and movements change the skeletal structure over time.

Regarding transient short-term memory, Barnes et al. (2009) observed changes in spectral characteristics of ongoing activity in task-related regions after a short n-back working memory task. These changes gradually returned to pre-task baseline values after several minutes, and recovery speed was dependent on working memory load of the task.

Notably, even in the absence of explicit or implicit memorization load recent cognitive experience alters intrinsic connectivity patterns for minutes after the exposure. Short engagement in a very simple visual classification tasks has been shown to increase functional coupling between frontal cortex and the respective category-selective visual areas (Stevens et al., 2010). Waites et al. (2005) report changes in functional connectivity to task-related areas after only ~5 min of silent language production. Even passive listening affects subsequent resting functional connectivity depending on language content (Hasson et al., 2009). Duff et al. (2008) observed changes in spectral characteristics of ongoing activity fluctuations within and beyond motor areas following an easy sequential finger tapping task without sensorimotor learning demands.

These findings indicate that ongoing activity patterns also express the system's memory of current or recent operational context. Electrophysiological observations in sensory cortices suggest that the functionally active synaptic circuitry, which ultimately manifests itself in specific patterns of spontaneous activity, is the result of a combination of sensory context, environmental contingencies, and experience (Fontanini and Katz, 2008). As a prominent example of task-related context, attention has been suggested to operate via changes to current network state (Harris and Thiele, 2011). The functional imaging results described above suggest that this principle likely extends to the dynamics in large-scale ICNs.

One consequence of this observation is that it becomes questionable whether a distinction between “true intrinsic” and context-induced functional connectivity in imaging studies is meaningful. If, as we argue, a major function of ongoing activity states were to encode the *interaction* of the current task and environmental setting with past experience, then such a distinction may not be easily possible.

This leads to methodological challenges regarding the study of functional connectivity *during* tasks. While the above dissociation between task-induced and “truly” spontaneous functional connectivity may be problematic, a different dissociation may be necessary for certain studies from a methodological point of view. This dissociation concerns functional connectivity (be it task-related or not) vs. co-fluctuations in task-evoked responses. Any given task causes evoked responses to individual trials or stimuli in a set of segregated regions. If these responses are not sufficiently well removed or regressed out from the signal time courses they may result in “trivial” apparent connectivity due to repeated task-induced co-activation of regions that may not be necessarily functionally interacting. Of course, this criticism speaks to the general problem of inferring functional connectivity in the sense of cross-regional communication from mere correlations. And although this point is particularly problematic in task settings, it may to some extent concern resting states as well. Of note, evoked responses show true (non-linear) interactions with varying ongoing activity levels rather than linearly adding up with them (see next section). This may render sub-optimal the approach of regressing out an estimated average task-evoked response. Several studies have investigated functional connectivity during task without removing evoked responses. For example, seed-based approaches have been applied with a specific interest in regions exhibiting correlated activity (evoked or not) to certain regions of interest during different cognitive tasks (Eckert et al., 2009). Another methodological approach to co-fluctuations during task is beta series correlation analysis that explicitly measures fluctuations in trial-by-trial evoked activity (Rissman et al., 2004), recognizing the functional importance of trial-by-trial variability. A very different approach for whole-brain characterization of connectivity during task has been global and nodal graph theory-based measures as applied to correlation matrices of the parceled brain, with (e.g. Fornito et al., 2012) or without regressing out evoked responses (e.g. Ekman et al., 2012; Moussa et al., 2011). In conclusion, whether or not evoked responses should be accounted for will depend on the experimental question at hand, while recognizing that a complete analytical segregation of evoked and spontaneous activity may remain beyond our reach simply because

the biological processes are not separable (see non-linear interactions discussed below).

Ultimately, investigating ongoing activity during task will be key to understanding its functional *raison d'être*. In the next section, we describe task studies that investigated functional consequences of fluctuations in ongoing activity amplitudes rather than cross-regional correlations of these fluctuations.

Intrinsic state impacts behavior

We argue in this review that ongoing brain activity is functionally meaningful. The obvious way of probing this claim is to study its influence on task-evoked responses and behavior. In the following, we will review functional imaging experiments that have done just that.

Fox et al. pursued this approach in the motor system. In a region of primary sensorimotor cortex activated during unimanual button presses they confirmed the commonly observed high trial-to-trial evoked-response variability. They also measured activity in the motor cortex ipsilateral to the hand performing button presses, i.e., contralateral to the primarily task-related motor region. This region was defined by intrinsic functional connectivity with the task-related motor cortex region. They used these measures as a proxy of ongoing task-unrelated activity and found that their fluctuations accounted for a substantial proportion of the evoked response variability in the functionally activated motor cortex (Fox et al., 2006). Moreover, in a subsequent analysis (Fox et al., 2007), they found that this variability was behaviorally relevant. They observed a significant relationship between evoked response levels (during the initial epoch of 2.2–4.3 s after button presses) of the functionally activated motor region and spontaneously occurring variability in button-press force generated by the participants (although it may not be straightforward how to interpret that lower ongoing activity levels were observed for harder button presses). This finding is important both from a physiological and a methodological perspective. Physiologically, it implies that ongoing activity fluctuations are functionally meaningful and translate into behavioral variability. In fact, this very variability is the ongoing network dynamic in action (Fontanini and Katz, 2008), and as discussed above, is the non-random manifestation of context and memory into the current operation. The methodological importance of this result lies in pointing out that analysis procedures that remove trial-to-trial variability in event-related responses only allow for a partial understanding of brain function and behavior and can in fact obscure the continuity and history of brain processes. Such methods assume the existence of a veridical evoked response that linearly adds onto uncorrelated background noise. This assumption is incorporated in conventionally applied event-related averaging, normalization to pre-trial baseline, and subtraction/regression of ongoing activity from time series. And commonly used general linear model approaches in functional imaging studies explicitly estimate a single evoked response amplitude over all repetitions of an event.

While Fox et al. studies show response variability to be behaviorally relevant, they still incorporate the basic assumption shared with general linear models that the relation between ongoing and evoked responses is inevitably additive. This assumption is subject to doubts regarding its validity because the behaviorally relevant early activity difference did not propagate linearly into the response peak as it should under this assumption. Another potential limitation to studies in the motor system is to consider activity in the contralateral motor cortex an estimate of ongoing activity that is not subject to any contamination by task-related activity. As stronger button presses are associated with co-innervation of more proximal upper limb musculature which in turn is more bilaterally represented than distal movements (Kleinschmidt and Toni, 2004), this effect in itself could contribute to the experimental observations in motor cortex ipsilateral to the task side.

These two points, additivity of evoked and ongoing activity and task-unrelated measures of ongoing brain activity, have been further

investigated in perceptual studies of the functional impact of ongoing activity on evoked and behavioral response variability. In previous sections, we have developed a line of argument according to which ongoing activity would be interpreted to represent an internal model of attributes and regularities in the world and that this model among other functions underlies prediction-based inference on the causes of sensory input. Perceptual tasks using ambiguous or near-threshold stimuli are therefore particularly well suited to harness the effect of functional context as set by the current network activity state. This is because as discussed above, internal representations can serve perceptual inference on often sparse and ambiguous sensory input in the real world.

Hesselmann et al. (2008a) asked participants to report their categorical percept on short presentations of Rubin's ambiguous vase-faces figure. The random and very long inter-trial intervals (20–50 s) un-obscured by evoked activity allowed using the prestimulus baseline level as a measure of ongoing activity directly in the task-relevant regions. Higher prestimulus ongoing activity level in the right FFA, a region specialized for face processing, was found to bias perception towards faces rather than a vase. The finding that higher spontaneous levels of activity in task-sensitive regions impact perception was confirmed in a motion discrimination task (Hesselmann et al., 2008b). Random-dot kinematograms were presented briefly at subject-specific threshold coherence and again at long random inter-trial intervals. This time, higher prestimulus activity levels in the right motion-sensitive area (V5/hMT+) significantly impacted decisions towards perception of coherent rather than random motion. In both studies, results were selective to the respective perceptually specialized regions and no other areas showed prestimulus differences between the alternative perceptual outcomes.

A functionally speaking crucial finding in both of these studies was the occurrence of interactions between ongoing and evoked activity, i.e., of a non-linear relationship. While predicted by several theoretical accounts (Buonomano and Maass, 2009; Friston, 2010), these observations were novel at the empirical level. In a seminal paper by Arieli et al. (1996) for instance, the contribution of spontaneous activity to evoked response variability was reported as substantial but appeared to respect linear additivity. In the anesthetized visual cortex the addition of an averaged evoked response onto trial-by-trial baseline activity levels very closely predicted the actual response observed on each given trial. On the contrary, the imaging studies discussed above (Hesselmann et al., 2008a,b) showed a significant interaction between evoked and ongoing activities when predicting perceptual outcome. Specifically, in the relevant areas (FFA or hMT+, respectively) the activity levels during the peak of the evoked response were less influenced by variations in prestimulus activity levels when faces rather than a vase were perceived, and when coherent motion rather than random motion was perceived. The basic mechanism here was hence a reduced baseline-to-peak signal increase during trials with higher as opposed to lower pre-stimulus activity. And this negative interaction between ongoing and evoked activity was stronger in trials where these areas were crucial for the perceptual decision (i.e. when faces or coherent motion were perceived; cf. Fig. 4 in Sadaghiani et al., 2010). In conclusion, the impact of ongoing activity on perception goes beyond a mere passive propagation of effects preceding stimulus presentation.

Interestingly, in the aforementioned motor study (Fox et al., 2007), evoked response peaks closely matched for hard and soft button presses in spite of different initial rising slopes (as also reflected in different activity levels of the contra-lateral motor cortex). This observation may indicate similar non-linearities during active movement (although the linear subtraction applied in that study assumes linear summation). A recent analysis of the same motor response dataset shows a reduction of trial-to-trial variability in widespread cortical activity during the evoked response as compared to pre-trial baseline, confirming the negative interaction of ongoing and evoked

activity (He, 2013). Similar to Fox et al. (2007) Schölvinck et al. (2012) measured ongoing activity in a region functionally connected to the stimulus-selective area, albeit in a different methodological approach using psycho-physiologic interaction. In this study where participants were asked to detect gratings at threshold visibility, the authors observed no interaction between ongoing and evoked activities, although they confirmed a significant effect of ongoing activity on perception. The authors speculate that in general non-linear interactions may occur in higher-level areas such as FFA and hMT+ (Hesselmann et al., 2008a,b) but not in primary sensory cortices such as V1 (Bianciardi et al., 2009; Schölvinck et al., 2012). Another factor likely contributing to whether or not non-linear interactions occur may be the general state, e.g. mainly linear effects during anesthesia (Arieli et al., 1996) or passive perception (Bianciardi et al., 2009) and possible non-linear effects during active perceptual decisions (Hesselmann et al., 2008a,b).

The interaction of stimulus-evoked and ongoing activity in sensory areas supports a prominent role of ongoing activity in the brain's constructive interpretation of sensory input. More differentiated analyses of this interaction (Hesselmann et al., 2010) suggest that ongoing activity in sensory cortex represents not only itinerant predictions about possible future perceptual contents but rather the convolution of predictions with "precision" or gain. Given the noise in environmental states or sensory input, optimal perception requires two distinct processes. The first is predicting the content of a percept (i.e. the cause of the stimulus). If this prediction is perfect, it "explains away" the sensory input. Any residual imperfection causes a prediction error. This prediction error is an evoked response that provides a signal to a higher hierarchical level indicating a need to change or refine the prediction and thus iteratively reduce the prediction error to zero (Friston, 2010). The second process involves properly inferring the uncertainty or precision of the prediction (i.e. the probabilistic context in which the stimulus appears). Precision is thus thought to modulate the amplitude of prediction error responses, in other words a gain control function (Friston, 2010). Precision is important because for instance attention can exploit this mechanism. Many naturally occurring prediction errors may be of little relevance to the individual and therefore the gain in processing them should remain low for economic reasons. Conversely, in some settings, if prediction error is highly relevant, it may be useful to amplify prediction error so as to permit a full "explaining away".

Regarding the functional nature of ongoing activity in sensory cortices, several observations suggest that the dynamics of perception are mainly determined by fluctuations in precision rather than predictions per se. First, deeply sagging levels in prestimulus activity of sensory cortices lead to false alarms. This finding is compatible with accounts of ongoing activity as precision-weighted prediction error but not with a view where cortical signal is a proxy of sensory evidence that if passing a threshold will entrain a perceptual decision (Hesselmann et al., 2010). Furthermore, under bistable rivalry conditions (such as Rubin's faces-vase figure discussed above) where the causes of sensory input (predictions) are known to the subject and remain identical, variability in perceptual outcome is likely governed by fluctuations in precision (Kleinschmidt et al., 2012). For a detailed discussion see Sadaghiani et al. (2010) and Kleinschmidt et al. (2012).

Perceptual outcome may be influenced by spontaneous activity in brain areas far beyond the focal stimulus-selective regions. In a somatosensory detection task, Boly et al. (2007) observed that prestimulus activity levels in large distributed systems resembling ICNs influenced whether or not threshold-level stimuli were perceived. The system biasing towards successful detection comprised areas of two cognitive control systems (cingulo-insular-thalamic and fronto-parietal, cf. Dosenbach et al., 2007). Conversely, high ongoing activity in areas of the default mode network biased towards missing the stimulus. In an auditory threshold detection task Sadaghiani et al. (2009) likewise observed a significant effect of ongoing activity

on perceptual outcome not only in stimulus-selective auditory cortex but also in a number of distributed ICNs. While higher ongoing prestimulus activity in the cingulo-insular-thalamic ICN as well as the default mode ICN biased towards successful detection, higher levels in the dorsal attention ICN lead to frequent misses. These two studies as well as the study by Schölvinck et al. (2012) that also observed perceptual effects from ongoing activity in cortex remote from the stimulus-selective site all involved threshold detection paradigms. It is likely that in such studies that involve all-or-none success of detection, ongoing activity from large-scale ICNs becomes functionally pivotal. Conversely, in perceptual *decision* studies that involve a choice between two closely matched alternatives, it would be the purely local ongoing activity variations in the perceptually crucial area that impact behavior (Hesselmann et al., 2008a,b). We conclude that the spatial pattern within which ongoing activity affects behavior is context-dependent and is detectable precisely at that position within a hierarchical ongoing activity structure that best matches the functional demands of a given context.

This conclusion also holds with respect to the sign of this impact that can be facilitatory or detrimental. The functional consequences of itinerant reactivation of any given network will depend on the role of that network in the context of the task at hand. As an example, high spontaneous activity levels in the default-mode network, commonly thought of as “task-negative”, may be facilitatory in certain task settings (Fornito et al., 2012; Sadaghiani et al., 2009, cf. discussion in Sadaghiani et al., 2010).

So far, functional consequences of intrinsic activity fluctuations have mainly been studied in simple perceptual decisions and motor behavior. Coste et al. (2011) reported that this mechanism is as relevant for higher cognitive functions such as top-down control. They used a Stroop color-naming task in which color-word interference on incongruent stimuli caused strong reaction time variability both within as well as across participants. Across individuals, sensitivity to prestimulus activity fluctuations in task-relevant regions scaled with the subject's cognitive susceptibility to Stroop interference. In terms of within-subject variability, in participants who showed reaction time slowing due to Stroop interference, ongoing prestimulus activity significantly differed between fast and slow responses. In sensory areas, the direction of this effect was again dependent on the functional role of the region in the particular task; while higher ongoing activity in task-relevant color-sensitive regions predicted fast responses, it biased towards slower responses in the task-interfering word-form area. Crucially, the strongest impact of prestimulus activity was observed in prefrontal cognitive control regions. In particular, prestimulus activity was higher prior to fast responses or successful cognitive control, in dorsal anterior cingulate and dorsolateral prefrontal cortices (dACC, DLPFC), the two regions most consistently implicated in Stroop task control (MacDonald et al., 2000). The inter-individual differences in these effects speak to the interpretation of itinerant background activity as exploration of the brain's “dynamic repertoire” (Ghosh et al., 2008) that keeps the brain malleable (discussed above). In subjects with greater behavioral interference effects, larger fluctuations in behaviorally relevant prestimulus activity likely reflect a greater range of dynamic exploration. In other words, the “rigidity” of mind set that underpins task compliance and optimally avoids interference effects in certain cognitive settings, may not be optimal under changing or incompletely transparent task requirements often encountered in the real world (Coste et al., 2011).

Conclusions

The study of ongoing brain activity fluctuations has had several remarkable consequences. A practical and relevant one is medical utility because resting state studies are feasible in patient populations that are difficult to study in activation paradigms. This application produces new insight into the relation between brain function and clinical

phenotype. Another consequence is methodological and expressed in the arrival of exploratory data-driven analysis techniques to complement paradigm-related approaches. Finally, from a neuroscience view, studies as those reviewed here have served to renew the interest in tracking continuous real-time brain activity records in relation to perception and action rather than charting average sequences of stimulus-driven or action-related activity changes. To some extent, this can be compared to the relation of constructivist and behaviorist views on brain function, where the former emphasizes a crucial role of active agency as in for instance inference in perceptual synthesis (Friston, 2010). The past trajectory of the brain's internal model is reflected in moment-to-moment ongoing activity states. These states are sensitive to current context and non-linearly interact with incoming sensory information. The presence of interactions renders a full separation of “true intrinsic” from context-induced and stimulus-evoked activity analytically virtually impossible, and conceptually incomplete. One important observation emerging from recent findings is that the intrinsic and spontaneous dynamics of brain activity seem to explore the space of possible brain states along very similar trajectories as those which can be induced by different task contexts. This observation, namely that ongoing brain activity is spatio-temporally highly organized into intrinsic functionally meaningful networks, has also mediated another shift of emphasis, from localizationist/segregationist views, which have dominated functional neuroanatomical studies for a long time, back to a greater appreciation of large-scale interactions and integration across brain regions.

Conflict of interest

Both authors declare that they have no conflict of interest.

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