



The relation of ongoing brain activity, evoked neural responses, and cognition

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Ongoing brain activity has been observed since the earliest neurophysiological recordings and is found over a wide range of temporal and spatial scales. It is characterized by remarkably large spontaneous modulations. Here, we review evidence for the functional role of these ongoing activity fluctuations and argue that they constitute an essential property of the neural architecture underlying cognition. The role of spontaneous activity fluctuations is probably best understood when considering both their spatiotemporal structure and their functional impact on cognition. We first briefly argue against a “segregationist” view on ongoing activity, both in time and space, which would selectively associate certain frequency bands or levels of spatial organization with specific functional roles. Instead, we emphasize the functional importance of the full range, from differentiation to integration, of intrinsic activity within a hierarchical spatiotemporal structure. We then highlight the flexibility and context-sensitivity of intrinsic functional connectivity that suggest its involvement in functionally relevant information processing. This role in information processing is pursued by reviewing how ongoing brain activity interacts with afferent and efferent information exchange of the brain with its environment. We focus on the relationship between the variability of ongoing and evoked brain activity, and review recent reports that tie ongoing brain activity fluctuations to variability in human perception and behavior. Finally, these observations are discussed within the framework of the free-energy principle which – applied to human brain function – provides a theoretical account for a non-random, coordinated interaction of ongoing and evoked activity in perception and behavior.

Keywords: ongoing activity, spontaneous activity, resting state functional connectivity, intrinsic functional connectivity, fMRI, prestimulus activity, variability, fluctuations

INTRODUCTION

Our review is based on the premise that – just as man-made architectures (and probably even more so) – the nature of biological systems is best understood by jointly considering their form and function. We will attempt to apply this view to ongoing brain activity. Our review of the form of ongoing or “spontaneous” brain activity will cover its temporal and spatial structure. Instead of attempting to be exhaustive in this respect, we will selectively emphasize some aspects mainly for two reasons; first, because we feel they may be under-represented in a field that is currently dominated by the notion of “resting state networks”; second, because we feel that these aspects are helpful when pondering the function of ongoing activity. In the second part of our review, function will then be the theme developed in more detail. We will focus on cognitive consequences of ongoing activity *fluctuations*, for the simple reason that they permit the most direct probes of functional significance for a phenomenon that is no longer fully “spontaneous” when bound into a context so as to measure function. Across this analysis of form and function we will then discuss how one theoretical framework, that of “free energy” introduced by one of us (Friston, 2005), may provide important clues for understanding the nature of ongoing brain activity. Our review will mainly concentrate on the human

brain and functional MRI. The latter has been informative due to its superb localizing power and its exquisite capability to record the dynamics of neuronal population activity across the entire brain and to hence capture large-scale functional connectivity patterns. Yet, for instance when addressing temporal properties as below, limitations of hemodynamic signals will lead us to also discuss electrophysiological findings as well as observations relying on invasive procedures that cannot usually be applied in human subjects.

THE TEMPORAL STRUCTURE OF ONGOING BRAIN ACTIVITY

One of the most prominent features of ongoing activity is the fact that it fluctuates over time. This in itself can give rise to interesting speculations regarding function. If one thinks of a car engine, where such behavior would be functionally deleterious, one might wonder whether, and if so how, such fluctuations can be associated with a functional benefit (McDonnell and Abbott, 2009). Let us first consider the formal properties of these temporal fluctuations.

Ongoing human brain activity recorded by local electrocorticography (Freeman et al., 2000) shows a power law scaling but also an embedding of discrete peaks reflecting band-limited oscillatory activity. Interestingly, power in these distinct frequency bands is in turn also modulated over time with a predominance of very slow

frequencies (Leopold et al., 2003; Nir et al., 2008). Descriptively, it has been shown that there is a coupling or nesting of the higher-frequency electrical activity into the infra-slow (usually defined as <0.1 Hz) fluctuations (Vanhatalo et al., 2004; He et al., 2010) but the mechanisms and directionality of this relation are not yet fully understood. Studies comparing invasive electrophysiological recordings with functional neuroimaging results have obtained evidence of coupling between hemodynamic signals and both slow cortical potentials (He et al., 2008) as well as power of high-frequency band-limited activity, both evoked and spontaneous (Nir et al., 2007; Shmuel and Leopold, 2008).

We conclude from these observations that the temporal properties of ongoing activity can serve to warn us against a preoccupation with the “millisecond range” when studying brain function. Yet, assuming a conservative stance, we also conclude that there is currently no reason for a rebound into a view where infra-slow fluctuations in a specific frequency range could be considered a distinct entity of neural processes, other than those active in the processing of, for instance, sensory events. Studies using fMRI have established an apparent predominance of slow fluctuations in ongoing brain activity but there are several caveats to be borne in mind. First, the issue of whether the actual neural activity reflected in the hemodynamic signals shows power law scaling as in electrical recordings is still being debated (Cole et al., 2010). It is certain that the low pass filter characteristics of hemodynamic signals only permit tracking of slow neural activity modulations, cutting off little above the range of the infra-slow frequencies. And there are additional concerns related to the fact that – in spite of quantitative differences – even “BOLD signal” variations from a water phantom can readily manifest power law scaling due to properties of the MRI scanner (Zarahn et al., 1997; but see also Fox et al., 2007). It has also not been established that the spatial pattern of functional connectivity depends on the temporal scale under consideration, other than obvious effects related to signal power.

Together, we suggest thinking of the presently available evidence as an indication that brain activity over time may display at least partially scale-invariant characteristics. Such pink noise or power law scaling is not a privilege of the brain or even of biological systems but a feature of many if not all complex systems (Mandelbrot, 1998). Its ubiquitous presence does not denigrate its importance though. Regarding the brain, several researchers have emphasized the importance of this temporal structure for endowing neural processes with an inherent long-term memory (Linkenkaer-Hansen et al., 2001; Buzsáki, 2006). The memory function in this view does not reside in a specific frequency range but merely has a holistic pattern. However, for an alternative opinion and a more differentiated discussion of these issues we refer readers to a recent review by Raichle (2010).

THE SPATIAL STRUCTURE OF ONGOING BRAIN ACTIVITY

Our main point in the previous section was to review the literature that safeguards us against a temporal “segregationist” view. We believe that there is a similar danger in the spatial domain. The reason why many laboratories have focused on infra-slow fluctuations is that due to their power and their at least partial distinctness from other, namely “noise” signal sources in functional neuroimaging, these fluctuations have proven useful for studying the spatial structure of ongoing brain activity. Such functional connectivity studies have

also focused on the only paradigm which permits an apparently unambiguous assignment of signal variations to ongoing brain activity; namely, the “resting state”. Despite concerns about contributions from technical and physiological noise, the rationale of these so-called resting-state functional connectivity studies has been validated by concurrent electrophysiological recordings. In particular, it has been established that slow fluctuations in power of band-limited oscillations can be directly linked to the ongoing activity fluctuations observed with fMRI (Shmuel and Leopold, 2008) and involve similar distributed spatial structures (Laufs et al., 2003).

With this functional imaging approach, it is now well established that spontaneous brain activity fluctuations are spatially organized into a largely reproducible structure. The emphasis in a (large) literature, whose review is beyond the scope of this article, has been to define anatomically such resting-state or intrinsic functional connectivity networks (ICNs). We will adopt the latter terminology because there is reason to believe that similar correlational structures persist even when subjects are exposed to vivid sensory stimulation (Golland et al., 2007). The definition of ICNs revolves essentially around two issues, that of constituent regions and that of boundaries. And this definition has relied on two approaches, one hypothesis-driven as exemplified in analysis of functional connectivity with a so-called seed region (e.g., Biswal et al., 1997; Greicius et al., 2003), the other data-driven as exemplified by independent component analyses (e.g., Beckmann et al., 2005). The ultimate goal of these analyses is to derive an anatomical segregation from the recordings of ongoing brain activity fluctuations. Notwithstanding a great degree of convergence and robustness across many different laboratories, both of these approaches have proven to be heavily influenced by user-dependent settings. What such settings usually express is the user’s expectation regarding the degree of modularity in ongoing brain activity. While some laboratories emphasize big dichotomies (e.g., Fox et al., 2006b; Golland et al., 2008), others seek to establish a fine-grained differentiation (e.g., Margulies et al., 2007).

In this context, we would like to emphasize that the actual data structure does not suggest clear-cut modularity but only a gradual differentiation. The reason for such graded modularity is that the correlational structure of ongoing activity is bound together in a hierarchy. This structure is probably best thought of as a tree with the underlying activity correlations displaying a hierarchy from global to local levels (Ferrarini et al., 2009). These levels of organization range from the entirety of gray matter as the trunk, over systems of regions as the branches to within-region correlations as the foliage (Marrelec et al., 2008; Meunier et al., 2009). In fact, the strong presence of variance shared across all local levels and reflected in global gray matter (Schölvinck et al., 2010) correlation has led to considerable confusion regarding the degree of diversification or antagonism that can be observed across different ICNs (Fox et al., 2009; Murphy et al., 2009). ICNs can be considered a mid-level cross-section of this hierarchical tree where regions within an ICN share a lot of variance and where this variance is sufficiently distinct from that expressed in other ICNs to draw a separating line. As a function of whether one emphasizes similarity or distinctness of local variations in ongoing activity, data-driven analyses will produce quite different numbers of ICNs (e.g., Varoquaux et al., 2010). In our metaphor, this corresponds to the distance of the cross-section from the ground.

As a consequence of the hierarchical organization of ongoing activity, raising the level of cross-section higher from the ground will yield more fine-grained subdivisions of networks both at anatomical and functional connectivity levels. As an example, the postero-medial part of the most extensively studied ICN, the default-mode network, has recently been subdivided into three precuneus parts and a posterior cingulate part on the basis of distinct large-scale intrinsic connectivity patterns, each of which suggest different functional roles (Margulies et al., 2009). Another example involves the difficulty in anatomical and functional definition of the so-called “task-positive” system. An initially useful step was to distinguish the “task-negative” default-mode ICN from “task-positive” regions, the latter referring to a large set of regions showing activation in most types of cognitive paradigms (Fox et al., 2005). Using seed regions in the dorsal attention network, the resulting intrinsic connectivity system was not confined to the dorsal attention system as defined in paradigm-based studies (Corbetta and Shulman, 2002) but due to shared variance also included anterior insula/frontal operculum, anterior prefrontal cortex, and infero-lateral parietal and frontal areas. These additional areas partially overlap with an added ICN, termed the fronto-parietal control system conceptualized to serve cognitive control (Vincent et al., 2008). Conversely, other studies dissected cognitive control functions into two distinct ICNs, a cingulo-insular-thalamic and a lateral parieto-frontal network for sustained vs. adaptive/executive cognitive control, respectively (Dosenbach et al., 2006, 2007; Seeley et al., 2007). These findings clarify that the hierarchically embedded levels of spatial structure in intrinsic connectivity range down to sub-network and ultimately sub-region correlations. In fact, albeit on a different temporal scale, such patterns can even be recovered within single areas, and align with their mesoscopic functional architecture (Kenet et al., 2003).

Over and above the issue of modularity, defining ICNs in terms of anatomical boundaries has also proven difficult. This difficulty is largely due to the fact that “networks” are not clear-cut and rigid sets of constituent regions. Rather, the term “network” should be thought of as a gradual clustering according to a similar activity profile. As such, this term can of course help to interpret, communicate and compare experimental results but should not mislead to consider networks as strictly segregated. The spatial patterns are susceptible to precise positioning of seed regions and it has for instance been demonstrated that there are fairly smooth transitional zones between ICNs (Cohen et al., 2008). Even though some of these difficulties may be due to the intrinsic spatial smoothness of hemodynamic signals rather than underlying neural architecture, such observations may account for observed discrepancies. With respect to the task-positive regions however, these difficulties also stem from the existence of an ensemble of several interconnected task-positive ICNs. Accordingly, the labeling issue becomes most critical for connection hubs such as the anterior insula (Sterzer and Kleinschmidt, 2010) which has been suggested to orchestrate activity across different ICNs (Sridharan et al., 2008). In addition to the ICNs discussed above, the anterior insula has also been characterized as a major node in a right-lateralized ventral attention system (Eckert et al., 2008). This latter system (Fox et al., 2006b) in turn widely overlaps with the aforementioned control systems, especially the lateral fronto-parietal subsystem. Together, we conclude that

similar to what we emphasized in the temporal domain, ongoing activity variations also show a nested structure in the spatial domain that expresses an embedding of modularity into a hierarchy.

THE FUNCTION OF ONGOING BRAIN ACTIVITY FUNCTIONAL CONNECTIVITY, STRUCTURAL CONNECTIVITY AND COGNITIVE CONTEXT

The difficulties in adequately capturing the spatiotemporal form of intrinsic brain activity that we have discussed in the previous section should not be thought of as mere empty battles of nomenclature. This form is important when pondering the function of intrinsic activity, and any proposal with respect to this function will be benchmarked against its potential for accounting for this spatiotemporal structure. The perspective that we have proposed in the previous section for functional connectivity is reminiscent of descriptions of structural brain connectivity and we have already appealed to these similarities in the tree metaphor (Bullmore and Sporns, 2009). A hypothesis about what determines the form of ongoing brain activity that ensues is that intrinsic functional connectivity simply reflects some neural “noise” that plays out on a non-random structural connectivity; and therefore takes on the shape of a limited set of spatial patterns (i.e., dynamics on structure). Indeed, computational simulations of functional connectivity using noisy input generate functional covariance patterns that reflect underlying structural circuitry (Sporns et al., 2000). And empirical evidence has been reported showing strong correspondence of intrinsic functional and anatomical connectivity (Skudlarski et al., 2008; Greicius et al., 2009). In more comprehensive investigations, at the level of the entire brain, this match has been confirmed but systematic quantitative analysis also revealed that it is not perfect. In other words, structural connectivity permitted only a partial prediction of the empirically observed functional connectivity (Honey et al., 2009). Of course, the imperfection in predicting functional from structural connectivity could simply reflect limitations in the methods applied for data acquisition and analysis. Yet, an important alternative hypothesis is that with underlying structural connectivity as a backbone functional connectivity is shaped by additional context-dependent modulation.

At first glance, this hypothesis seems to be at odds with the persistence of spatial ICN patterns across different levels of context and consciousness, from task- and stimulus-induced active states (Fair et al., 2007; Golland et al., 2007; Eckert et al., 2008), over resting wakefulness (Greicius et al., 2003; Fox et al., 2005; Fransson, 2005), light and deep sleep (Horowitz et al., 2007, 2009; Nir et al., 2008), light sedation (Greicius et al., 2008), to deep anesthesia in monkeys (Vincent et al., 2007) and severe disorders of consciousness as in vegetative state patients (Boly et al., 2009). Furthermore, the finding of robust intrinsic activity patterns in the absence of consciousness also suggests that intrinsic activity fluctuations cannot be considered merely or entirely the neural correlates of conscious, mentation or mind-wandering that in the absence of an explicit task paradigm simply remains experimentally uncontrolled (Buckner and Vincent, 2007).

However, evidence in favor of the hypothesis that ongoing brain activity is in fact context-sensitive has now been accumulated by a range of studies. Although functional connectivity patterns persist qualitatively across wide ranges of different functional contexts, as mentioned above, they do nonetheless express quantitative

changes. They differ for instance quantitatively between the healthy awake brain and the brain in a state of pathological unconsciousness, where functional connectivity within the so-called default-mode network decreases with the degree of consciousness; across minimally conscious state, vegetative state and ultimately coma (Vanhaudenhuyse et al., 2010). They also differ quantitatively in the healthy brain between wakefulness and deep (slow-wave) sleep, a state of physiological unconsciousness (Horowitz et al., 2009). It is noteworthy that the reduction in connectivity between posterior and frontal areas of the default-mode network during sleep is anatomically selective, and that fluctuation amplitudes within regions remain unchanged. This result makes it unlikely that modulations in intrinsic connectivity simply reflect a change of noise levels propagating through an anatomically connected system.

And even during the state of wakefulness (and on a shorter time scale) intrinsic connectivity patterns express differences that can be related to recent cognitive experience. Over the course of one scanning session, i.e., a time span that in all likelihood does not involve gross structural connectivity changes, adaptive modulation of intrinsic functional connectivity has been reported after visuo-motor learning (Albert et al., 2009), episodic memory (Tambini et al., 2010) and language tasks (Waites et al., 2005; Hasson et al., 2009). These findings show that functional context interacts with the expression of intrinsic activity and thus motivates further experimental investigation of the functional significance of intrinsic activity.

A common critique of these latter studies is that they might collapse “true intrinsic” activity with reverberating traces of previous cognitive experience. Of course, the same critique holds for “pure” resting-state studies during wakefulness, because they at least include task-unrelated mind-wandering that constitutes an ongoing cognitive content (Mason et al., 2007; Christoff et al., 2009) and by its very nature cannot be considered to lack context. The only way to dissociate “true intrinsic” activity from more specifically context-related neural processes would be if there were spatiotemporal hallmarks selectively tagging intrinsic activity. Our review of its temporal and spatial form, however, suggests, at least to us, that no such properties can currently be identified with confidence. Alternatively, one may question whether such dissociation is inevitably justified and necessary and this leads one to consider the actual function of ongoing activity. We propose that its function is intimately related to cognition, and this relation is inherent to the brain, be it in a “resting” or active state. This proposal could seem at odds with the studies that we have discussed above and that show qualitative spatial correspondence between ICNs across very different functional brain states. But it is as true that ICNs strongly resemble spatial patterns with sets of regions that typically co-activate (or deactivate) in cognitive activation studies as a function of the paradigm (Smith et al., 2009). We therefore argue that function cannot be assigned purely on the basis of spatial patterns.

COGNITIVE CONSEQUENCES OF SPONTANEOUS ACTIVITY FLUCTUATIONS

In this section, we review a different way of addressing the function of ongoing activity. In this approach, the functional consequences of ongoing activity are assessed by studying whether fluctuations

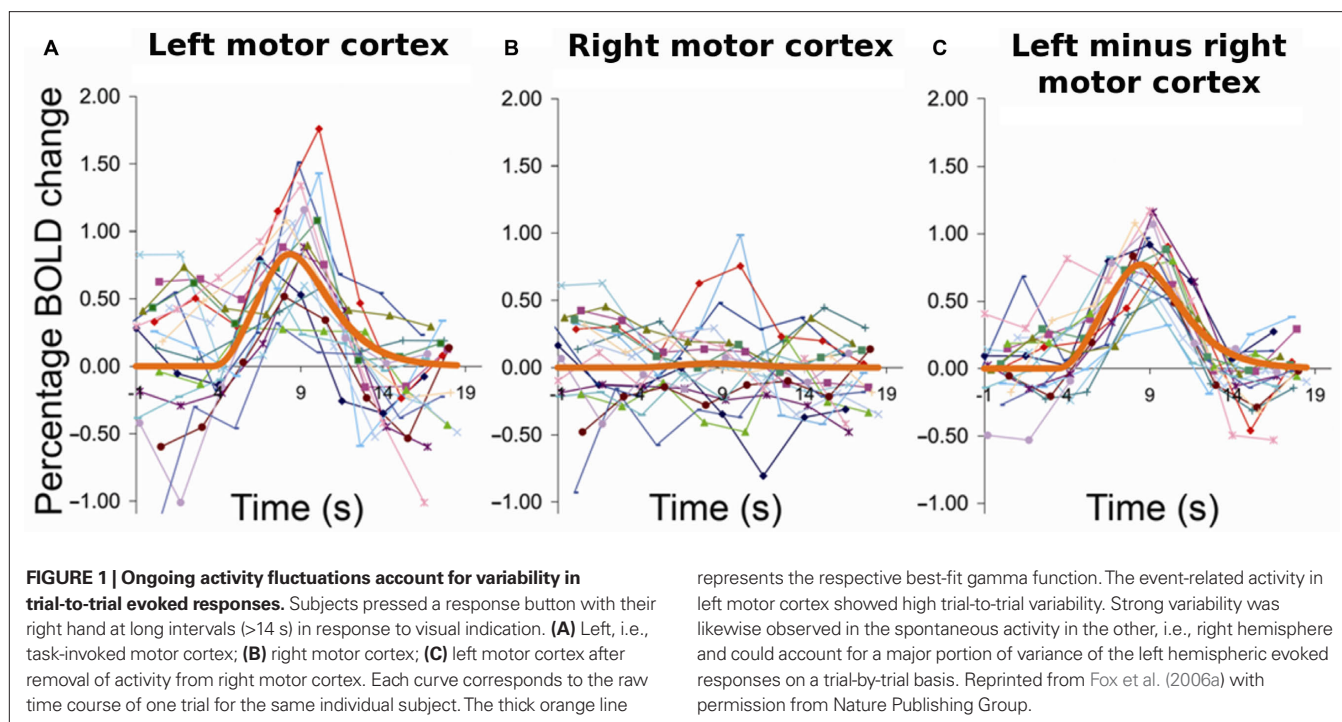
in ongoing activity can account for behavioral variability. From the previous sections we can derive the following predictions for such an account: (1) ongoing activity should affect behavior with a time constant that is sufficiently slow to be captured by hemodynamic signals. (2) The spatial pattern within which ongoing activity affects behavior should be context-dependent and should be detectable precisely at that position within a hierarchical structure that best matches the functional demands of a given context. In the following, we review evidence for both predictions from recent neuroimaging studies.

Two lines of earlier research suggested that there might indeed be a link between ongoing activity fluctuations and behavioral variability. One is that behavioral performance when repeating the same task over and over again shows fluctuations with a qualitatively similar temporal profile as ongoing activity, i.e., high power at low frequencies (Gilden, 2001). The other is that neural responses evoked by identical stimuli fluctuate over time. The latter effect has been very explicitly tied to ongoing activity fluctuations by examining the dependence of evoked response variations on trial-by-trial fluctuations of pre-stimulus activity levels. In an influential study, Arieli et al. (1996) investigated ongoing and stimulus-evoked activity with concurrent optical and electrophysiological methods in anesthetized cats. They found that variability of evoked responses could be largely accounted for by the initial level of ongoing activity just prior to stimulus onset. Their data show a linear relationship between ongoing activity immediately before stimulation and evoked activity levels. Simply adding the averaged stimulus-related activity increment to the pattern of ongoing activity in an individual trial provided an excellent prediction of the actually measured activity level during the evoked response in that trial. Recently, several functional neuroimaging studies have not only revisited this issue but also established links between neural and behavioral variability.

Functional imaging findings

At a very different spatial and temporal resolution than Arieli et al., Fox et al. (2006a) made a similar observation using fMRI. They found that trial-to-trial variability of finger movement-related activity in motor cortex could be largely accounted for by ongoing activity fluctuations measured in the contralateral motor cortex, the one ipsilateral to the finger that was moved (Figure 1). Their clever approach tackled the problem that the relative contribution of ongoing and task-related activity cannot be separated by analyzing activity in the task-relevant region during the evoked response. By removing trial by trial the simultaneously recorded activity level in a region that belongs to the same ICN but was not engaged by the task from the signal in the task-relevant region they “cleaned away” the ongoing and retained the evoked component.

From the perspective of data analysis in functional imaging, this procedure is very attractive. It suggests that averaging across trials provides a good way for estimating a veridical evoked activity change, the response, and that the latter shows little if any variability. And removing the variability related to ongoing activity and hence tightening the residual variability of the evoked response estimate yields a clear-cut gain in statistical sensitivity. Yet, the same group established in a subsequent study that the trial-by-trial variability



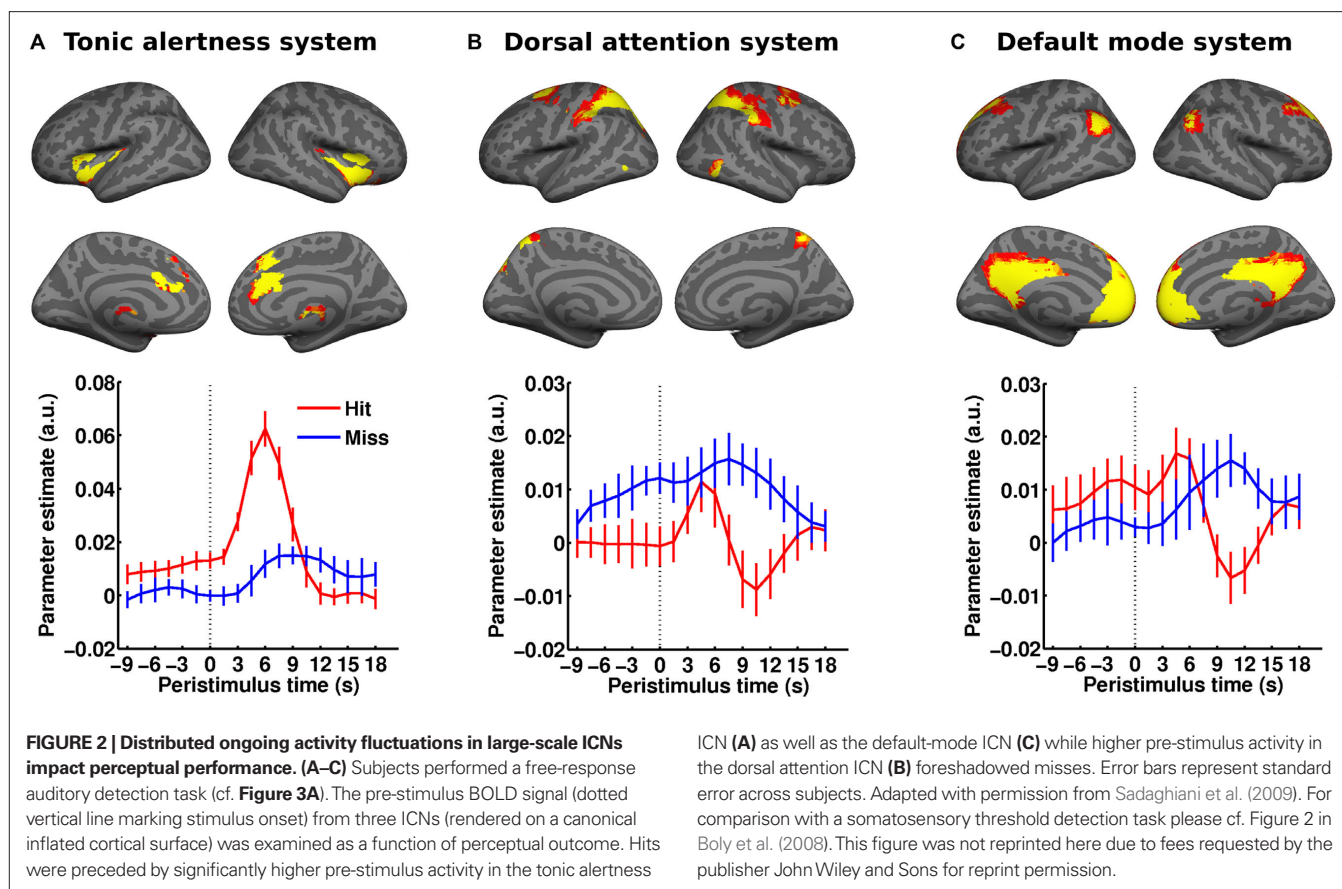
in task-related motor cortex activation was functionally meaningful and translated into behavioral variability as measured by the force that subjects applied in different trials when pressing a response button (Fox et al., 2007). In other words, the aforementioned procedure of removing inter-trial variability, albeit attractive from a signal processing perspective, is far less tempting for that line of research which seeks to establish neural correlates of behavior.

From a methodological point of view, a limitation of the aforementioned approach is that it is grounded in the assumption that motor cortex ipsilateral to the moving finger is silent in this paradigm. Indeed, distal upper limb movements are represented almost exclusively contralaterally but with greater force they involve co-innervation of more proximal musculature, which in turn is represented more bilaterally in motor cortex (reviewed in Kleinschmidt and Toni, 2004). Other groups have therefore explored alternative approaches to the issue of whether ongoing activity fluctuations are functionally relevant. Instead of using simultaneously recorded signal in a region that belongs to the same ICN but is silent in a task context, several groups have taken pre-stimulus signal in the same region that will subsequently respond to a given stimulus as a measure of ongoing activity. This approach is hence similar to the one adopted by Arieli et al. (1996) but on a different time scale.

Boly et al. (2007) investigated the perceptual impact of pre-stimulus activity fluctuations in a somatosensory detection task. For somatosensory stimuli close to perceptual threshold pre-stimulus activity levels in large distributed systems resembling ICNs indicated whether or not a stimulus was perceived on a given trial. The system biasing towards perceiving the stimulus comprised the thalamus, dorsal anterior cingulate cortex (dACC) and anterior insula/inferior frontal gyrus, as well as parieto-frontal areas including intraparietal sulcus and dorso-lateral prefrontal cortex. As discussed in the previous section, these areas commonly show activation or

“task-positive” behavior in a wide range of cognitive task settings (Corbetta et al., 2002; Smith et al., 2009). Conversely, on trials where subjects missed the threshold stimulus, pre-stimulus activity levels were higher in posterior cingulate (PCC), parahippocampal and lateral parietal components of the default-mode network. This latter network is known to show deactivation or “task-negative” behavior in most task settings (Gusnard and Raichle, 2001).

Taken together, these observations could further support a simple dichotomy in which higher ongoing activity in “task-positive” brain networks would facilitate perceptual performance whereas higher activity levels in the default-mode network would degrade performance. A recent study speaks against the generality of this scenario by showing that functional context determines in which brain regions ongoing activity will affect perceptual performance and whether this will be a facilitating or detrimental effect (Sadaghiani et al., 2009). In a free-response, auditory detection task, we presented broad-band noise stimuli in unpredictable intervals of 20–40 s and at individual detection threshold. Subjects pressed a button whenever they perceived the target sound. Successful detection as compared to misses was preceded by significantly higher pre-stimulus activity in early auditory cortex (Figure 3A) as well as in two ICNs. Perceptual performance was better with higher pre-stimulus activity in a network comprising thalamus, anterior insula and dACC, which suggests a role for this ICN in maintaining alertness and task-set (Figure 2A). Conversely, and counter to common intuition, higher baseline activity in the dorsal attention system of parietal and frontal areas biased towards misses (Figure 2B) presumably expressing the lack of spatial connotation in our stimulus and task. The observation of opposite effects in these two task-positive ICNs shows that in spite of shared variance, the networks are sufficiently segregated to exert independent influences on perceptual outcome. And finally, higher baseline activity in



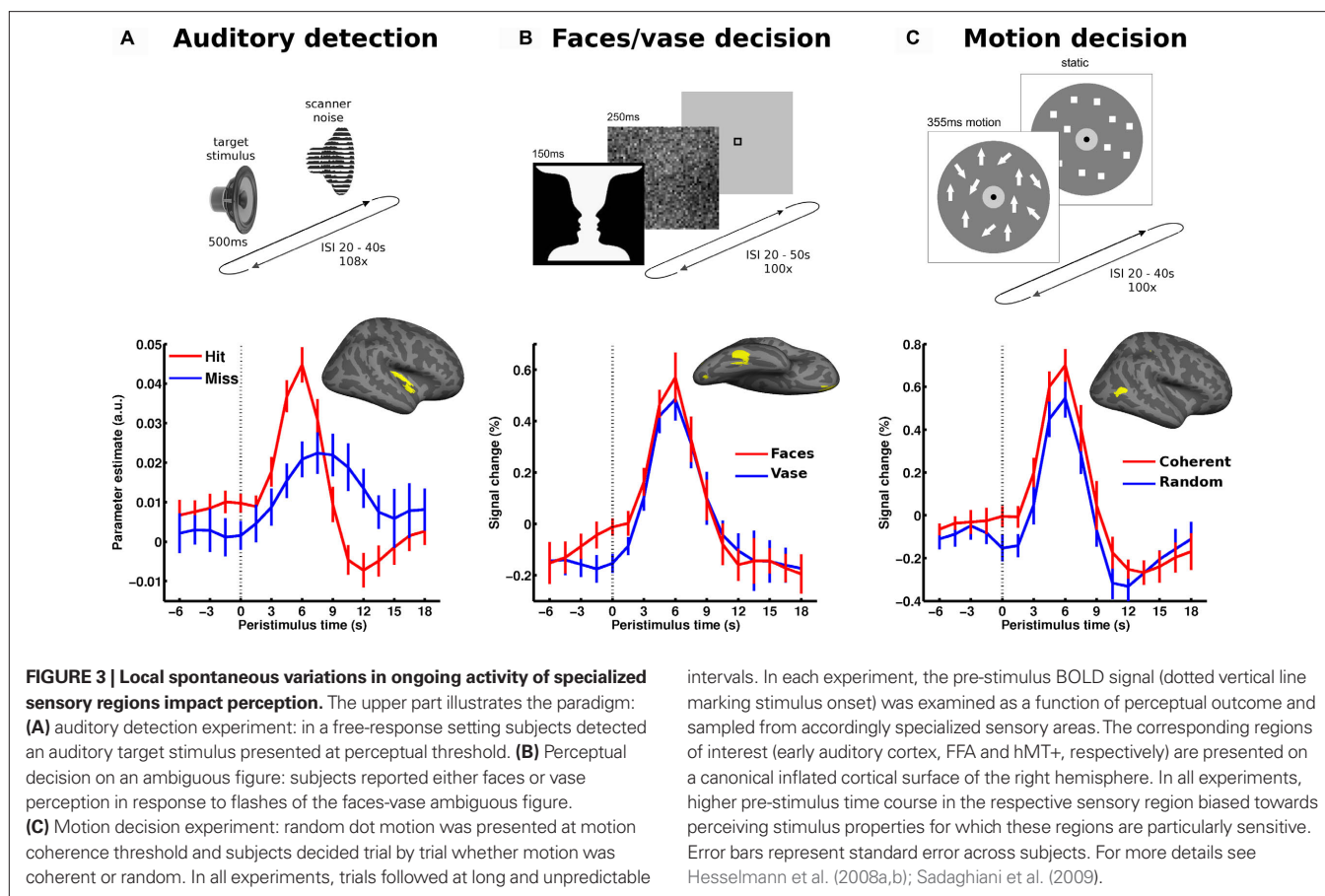
the precuneus/PCC region of the default-mode network preceded hits, which in turn yielded a biphasic response with a “task-positive” activation component preceding the typical but delayed deactivation (**Figure 2C**). At first glance, this finding might appear at odds with the existing literature but it probably reflects the importance of retrieving a memory template of the target for successful performance on the continuous sensory input (Shannon and Buckner, 2004; Daselaar et al., 2009).

Thus, in the context of a non-localized and non-semantic auditory stimulus and a task that depends on recognition memory but not spatial attention, the usual effects from activity in default-mode and dorsal spatial attention systems were reversed. Of note, the time courses of pre-stimulus effects in these two networks were very distinct, making it unlikely that signal change in one was simply (epiphenomenally) mirrored by that in the other. In other words, these opposite effects were presumably independent of one another rather than reflecting a hard-wired antagonism between these two ICNs that others have claimed based on the observation of intrinsic anticorrelation (Fox et al., 2005). These findings highlight that context determines the influence ongoing fluctuations exert on stimulus processing and ultimately perception.

It seems fair to posit that where and how ongoing activity fluctuations impact on perceptual decisions depends on which sensory features and cognitive faculties are relevant in a given context. Accordingly, one might expect that in perceptual decisions, which do not involve an all-or-none success of detection but a choice

between two closely matched alternatives, generic contributions from ICNs become less important and that a pre-stimulus effect might only be detectable in a single task-relevant region (rather than throughout the entire network to which this region belongs). In this case, it would be purely local variations in activity and not those throughout a distributed system that would exert an influence (cf. previous section on hierarchical structure of ongoing activity). Such a mechanism would make it mandatory to estimate ongoing activity from pre-stimulus signal in the task-relevant region instead of from simultaneous signal in a reference region of the same ICN. Evidence for such a scenario has been provided by two separate but closely related experiments.

In a perceptual decision task on Rubin’s ambiguous vase-faces figure, subjects had to report on each trial whether they perceived the vase or the two faces in profile. The presentation of the stimuli was sparse at long and variable intervals (range 20–50 s), and the stimuli were presented only briefly (Hesselmann et al., 2008b). Subjects reported face percepts on approximately half of the trials and vase percepts on the other trials. Higher pre-stimulus activity levels in the right fusiform face area (FFA), a region specialized for face processing, were found to bias towards the percept of faces rather than a vase (**Figure 3B**). This finding was later replicated in the domain of visual motion perception (Hesselmann et al., 2008a). In this study, short events of random dot motion with near-threshold coherence levels were presented, and subjects indicated on each trial whether they perceived coherent or random motion. Here, subjects’ perceptual decisions were biased by



pre-stimulus activity levels in right middle temporal cortex (V5/hMT+), a region crucially involved in the analysis and perception of wide-field coherent motion. Specifically, perception of coherent motion was preceded by significantly higher ongoing activity in V5/hMT+ (Figure 3C). In both experiments, no other task-related cortical regions showed a significant link between pre-stimulus activity and perceptual outcome.

Electro- and magnetoencephalographic findings

Electro- (EEG) and magnetoencephalography (MEG) studies have also established links between ongoing activity and behavior. While less informative in terms of spatial localization, these studies have identified distinct oscillation bands that carry signals, which predict perceptual performance. Using MEG, Jensen and colleagues observed that visual discriminability of a threshold stimulus decreased with an increase in pre-stimulus occipito-parietal α band power (van Dijk et al., 2008). Likewise, they reported that in a go no-go task false alarms were preceded by higher levels of α band power in the occipital cortex and bilateral somatosensory cortices (μ rhythm) as compared to correct withholds on no-go trials (Mazaheri et al., 2009). Not only responses to natural stimuli but also to artificial direct cortical stimulation are influenced by the power of ongoing oscillations: Using transcranial magnetic stimulation, phosphene-perception was only induced following lower pre-stimulation α amplitudes (Romei et al., 2008), suggesting that occipital alpha power indexes cortical excitability. Evidence link-

ing such observations in EEG frequency bands to the infra-slow frequency range covered by imaging studies comes from work by Palva and colleagues. They investigated pre-stimulus power fluctuations using full-band EEG sensitive to infra-slow fluctuations (<0.1 Hz) in a somatosensory threshold detection task within a free-response setting. They found highest detection rates and shortest reaction times to be associated with intermediate power levels (inverse u-shaped relation) of α , β and γ band oscillations over sensorimotor cortices, and with highest power of these bands over parietal electrodes (Linkenkaer-Hansen et al., 2004). Interestingly, in this task setting the phase of infra-slow fluctuations was found to be strongly correlated to the power of higher frequencies (1–40 Hz) and to be highly predictive of hits and misses on a trial-by-trial basis (Monto et al., 2008). Recently, electrophysiological studies have not only shown power but also phase of band-limited oscillatory activity to affect perceptual performance. For example, trial-to-trial variability in perceptual outcome has been related to the phase of EEG α and θ band oscillations in visual threshold detection tasks (Busch et al., 2009; Mathewson et al., 2009).

THE RELATION OF ONGOING AND EVOKED NEURAL ACTIVITY

The above findings are important because they show that across many temporal scales variability in ongoing activity – which is commonly obscured by normalization to pre-stimulus baseline – contributes to the way in which the brain (and ultimately, the observer) responds to sensory stimuli. The imaging studies show that the topography of

these effects is compatible with a hierarchical view on intrinsic brain activity and depends on context. In the two experiments discussed above, which involve fairly subtle perceptual decisions, we targeted areas that we considered likely to respond more strongly during one of the two possible perceptual interpretations of the ambiguous stimuli used. Despite identical sensory input in each experiment, we indeed confirmed that face-percept trials using the Rubin stimulus yielded higher evoked FFA responses and coherent-percept trials using the dot motion stimulus higher evoked hMT+ responses (Figures 3B,C). Together with the aforementioned effects observed in pre-stimulus signal these findings could be believed to confirm a behavior equivalent to the one in the study by Arieli et al. (1996) that we discussed above. In other words, a single stimulus would, on each trial, evoke a fixed activity increment which would add to the level of ongoing activity encountered on that trial. Variations in ongoing activity would then determine perceptual outcome by yielding variations in peak activity that would, or not, pass a threshold required for a perceptual decision. By such a mechanism, even a simple additive relationship between ongoing and evoked activity could become functionally significant (note that we have to call on a threshold mechanism – which is by definition non-linear – to make a linear effect of ongoing activity functionally interesting).

The important consequence from such a mechanism – that also provides an easily testable hypothesis – would be that the relation between ongoing and evoked activity should not depend on perceptual outcome because the latter would be determined solely by the peak activity of the response. We could reject this hypothesis in both experiments by showing a significant interaction between evoked and ongoing activity when predicting perceptual outcome. Specifically, peak and pre-stimulus activity levels in hMT+ correlated less when dot motion was perceived as coherent rather than random (Figures 4A,B). Likewise, peak activity levels in FFA were significantly less correlated with pre-stimulus signal when subjects perceived faces than when they reported a vase (Figures 4C,D). These observations show that the mechanism by which ongoing activity affects subsequent perception is independent from the one that can be observed during stimulus processing. In other words, the latter does not result from a mere passive propagation of effects preceding stimulus presentation. The theoretical implications of these findings for models of perceptual decision-making have been discussed in the respective publications (Hesselmann et al., 2008a,b). Yet, there is reason to believe that both linear (e.g., under anesthesia, Arieli et al., 1996, or in passive viewing, Bianciardi et al., 2009) and non-linear interactions can be observed and future work will need to clarify which parameters determine the regime under which ongoing and evoked activity interact (see Kislley and Gerstein, 1999, for a study on changes in linearity as a function of depth of anesthesia).

THE NATURE OF ONGOING BRAIN ACTIVITY

Comparing spontaneous fluctuations and variability after cueing

We have argued above that ongoing activity is modulated by cognitive context and that spontaneous activity fluctuations can be thought of as fluctuations of an internal and predictive contextual representation. It therefore appears sensible to compare results from such studies with those where context has been explicitly modulated by introducing cues that prepare for an upcoming cognitive challenge. Several studies have employed such cues to study the

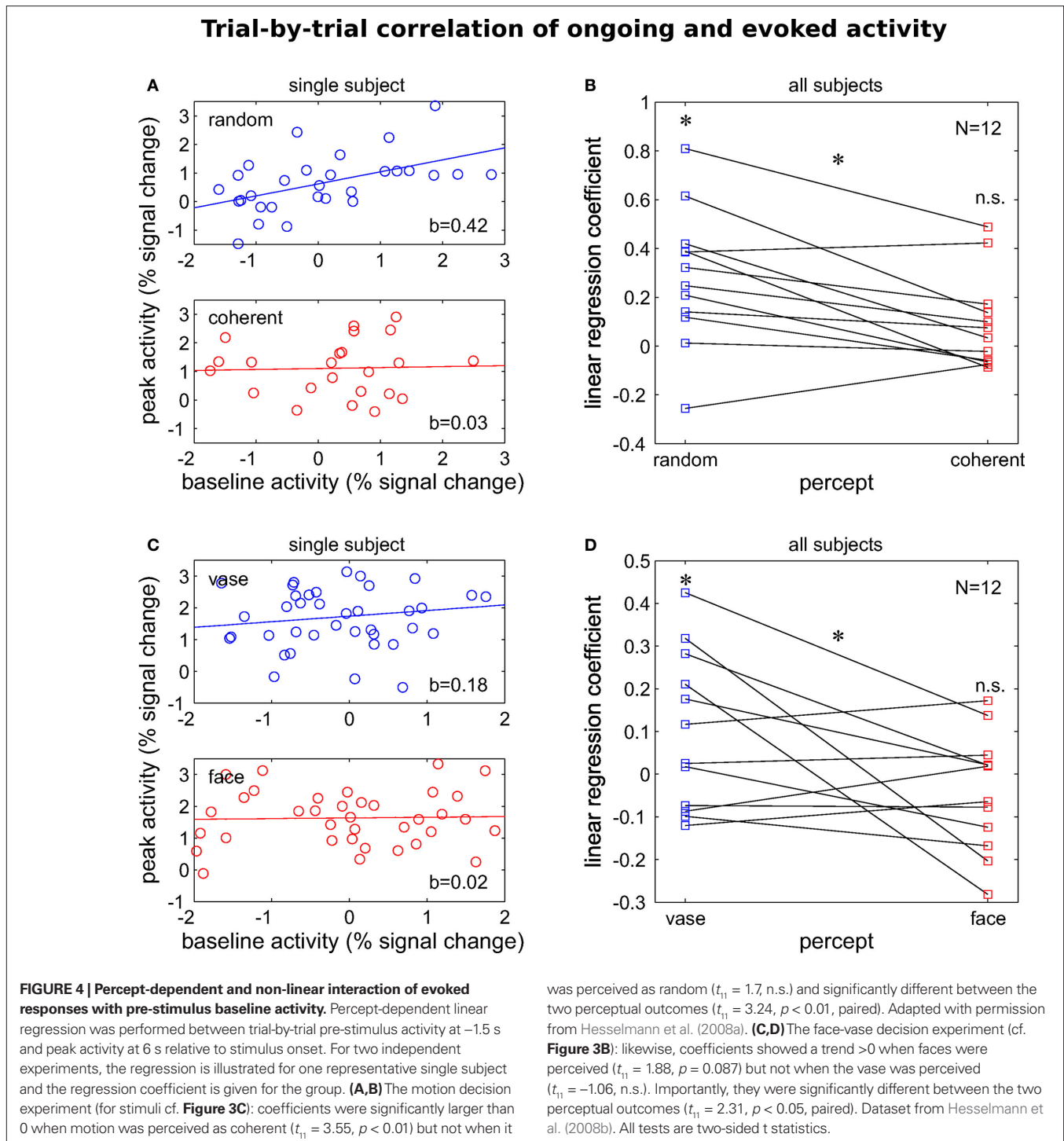
variability of evoked neural and perceptual responses to a single stimulus (or a group of equivalent stimuli) (Super et al., 2003; Sapir et al., 2005; Thut et al., 2006; Wyart and Tallon-Baudry, 2009). Typically, in these paradigms, a cue will appear that can indicate a task-relevant location or feature for a stimulus that will be presented after a brief but often variable delay. These studies in general try to understand which neural mechanisms underpin selective attention. As behavior and evoked responses are modulated by attention, variability in a cue-induced anticipatory signal that correlates with perceptual performance on the subsequent stimulus can be considered a neural signature of preparatory attention. Of course, this interpretation does not speak to the mechanism that generates this variability in the first place but only suggests that attentional preparation is subject to a variability of an unknown origin that is behaviorally relevant. The similarity of this conclusion with that from the aforementioned studies on spontaneous fluctuations suggests a need for closer examination and comparison.

From our perspective, variability in cortical activity following an orientating cue presents a special case and currently remains ambiguous. One interpretation could be that this variability is the same as that seen in ongoing activity and that the cue will hence be more or less efficient, both neurally and perceptually, as a function of the state of the system prior to cueing. Another view could be that the neural response elicited by the cue could in itself be variable and that this variability translates into perceptual performance. As we have discussed previously, simply removing the effects of pre-cue baseline would not permit arbitrating between these two scenarios, since the amplitude of the cue response may be subject to interactions with pre-cue activity levels. However, analyses as those reviewed above that preserve pre-cue “baseline” signal fluctuations could be used to disambiguate the functional nature of cued settings.

Another line of comparison regards the interpretation of the cortical signal. If the pre-stimulus signal expresses a level of preparatory attention in studies using cues, does this permit the conclusion that in studies without cues fluctuations of ongoing activity can be thought of as fluctuations in attention? If one were to make this claim it would have to survive a couple of benchmark checks. The most important one is that evoked responses to target stimuli should be enhanced by attention. This enhancement could reflect anything between a true response gain as implied in earlier studies (Chawla et al., 1999) and a simple additive effect of fixed stimulus-driven increment in the presence of an increased background activity (Sylvester et al., 2009). In both our studies addressing signal variations in the absence of cues, however, the opposite behavior was found. The higher pre-stimulus signal was, the smaller the actual incremental evoked response amplitude in regions that were critical to the percept on those trials, i.e., V5/hMT+ for motion coherence detection (Figures 4A,B) and the FFA for face perception (Figures 4C,D).

Predictive coding and free-energy formulations

So how can these observations about intrinsic fluctuations be understood functionally? We will address this under a predictive coding account of neuronal activity, given that cues furnish exogenous and explicit predictions. In what follows, it is important to realize that optimal predictions or expectations rest on two distinct processes. The first is predicting the content of a percept (e.g., what caused



the stimulus) and the second is properly inferring the uncertainty or precision of that prediction (e.g., the probabilistic context in which a stimulus appears). This difference is illustrated nicely by the difference between the effects of cueing and priming.

Cues are usually employed in attentional paradigms to guide predictions about task-relevant locations or features (context) but not about the actual target (content). In other words, knowing that a target will appear at a given location within the next couple of

seconds does not provide any information about the content of the target's features; e.g., whether a grating will be slanted to the left or right. Cues call for allocation of attentional resources to the appropriate sensory channels, without biasing to one outcome in these channels, or another. In what follows, we consider this in terms of optimizing the synaptic gain of selected channels. This may also help understand the electrophysiological correlates of non-spatial attentional or perceptual processes; e.g., related to the feature

class, in contrast to spatial attention (Wyart and Tallon-Baudry, 2009). Conversely, sensory priming induces expectations about the content of sensory input, which we will assume is mediated by priming-dependent changes in synaptic activity and efficacy. In accord with this view, priming effects are associated with reduced evoked response amplitudes and are, of course, readily embraced by predictive coding accounts (Henson, 2003).

Recently, it has been proposed that a single fundamental principle might govern brain activity underlying action, perception, attention and learning (Friston, 2005, 2009, 2010). In its most simple form, the free-energy principle states that the brain seeks to minimize surprise (more formally, the negative log-probability of a sensory outcome). This is achieved by continuously updating an internal model that generates top-down predictions of sensory input. Unexpected sensory inputs that cannot be “explained away” by an internal model of the current states of the world emerge as bottom-up prediction errors (hence predictive coding). These prediction errors are accumulated or assimilated by higher cortical areas to update the model and optimize its predictions. Perception rests on the optimization of top-down predictions (or, model) to best explain away the bottom-up prediction error caused by incoming sensory information, a notion embraced by Bayesian formulations (Kersten et al., 2004; Hohwy et al., 2008). In the present context, the free-energy formulation is of interest because it covers many observations about evoked responses but it is not confined to them. When applied to the specific issue of ongoing cortical activity and its relation to evoked responses (and subsequent perception), the free-energy principle can account for many reported empirical findings and yields further testable predictions.

The free-energy formulation (Friston, 2009) requires the brain to represent the causes of sensory input (by optimizing synaptic activity; i.e., perceptual inference), and its internal model of contextual and causal regularities (by optimizing short and long-term changes in synaptic gain and efficacy; i.e., attention and perceptual learning). Crucially, all changes in synaptic activity, gain and efficacy minimize the same thing; namely free energy, which under some simplifying assumptions is just the amount of prediction error. In line with this view, Lewis et al. (2009) observed that intensive training shapes intrinsic connectivity between visual areas and higher order frontal and parietal regions that presumably generate visuospatial top-down predictions. In terms of the distinction above, synaptic (neuronal) activity encodes the content percepts, while synaptic gain encodes contextual precision (cf. attentional gain). In what follows, we will consider ongoing activity as reflecting neuronal activity that predicts the causes of sensory inputs and then turn to interpretations that cover fluctuations in synaptic gain or precision.

Ongoing activity and predictions

Perceptual inference and learning speaks to a general principle, according to which past experiences inform predictions of the future to optimize behavior. The idea that ongoing activity patterns reflect a historically informed internal model of causal dynamics in the world (that serves to generate predictions of future sensory input) fits nicely with the role of neural “replay” in memory formation (Jeffery, 2004; Foster and Wilson, 2006). Indeed, the itinerant (wandering or searching) dynamics that characterize

intrinsic fluctuations have been proposed as mathematical models of short-term memory (Bick and Rabinovich, 2009) and have been discussed explicitly in terms of free-energy minimization (Kiebel et al., 2009b).

It is important to realize that this interpretation does not restrict the role of ongoing activity to brain states that are accessible to introspection. The most basic version of this mechanism might be seen during the perception of music and speech, where, mathematically, the itinerant dynamics conform to stable heteroclinic channels that show winner-less competition (Seliger et al., 2003; Kiebel et al., 2009a). However, these dynamics also manifest in the absence of sensory information – just because sensory inputs are not currently available does not mean that the brain models the world as having stopped. Important examples here include optimization (consolidation) of synaptic strengths during sleep (Vyazovskiy et al., 2008; Diekelmann and Born, 2010). Another example is optimization or selection of competing internal models, using itinerant searches over different hypotheses (models) about the world. This view links itinerant (*wandering*) dynamics to “mind wandering” often invoked to explain resting-state fluctuations. This link provides a formal and precise role for ongoing itinerant activity that has been exploited in perception (e.g., Kiebel et al., 2009a) and planning (e.g., Namikawa and Tani, 2010). In machine learning and robotics, the itinerancy mandated by sensitivity to initial conditions and some forms of chaotic dynamics is now one of the main candidates for explaining how trajectories into the future are explored and selected. This fits comfortably with the notion that brain activity can be formulated in terms of itinerant dynamics (e.g., Tsuda, 2001). One important feature of itinerancy is that it enables ongoing activity to express fluctuations that ensure transitions between different (meta)stable neuronal states (Deco et al., 2009). Itinerant fluctuations of this activity reflect the dynamic nature of the underlying internal model that does not remain locked in a stationary mode but remains malleable by continuously exploring hypotheses regarding future experience and action. It is for this reason that functional connectivity measures, which describe the extent of wandering activity (and not stationary activity levels), provide such an informative description. Similar neural population behavior has also been observed on shorter temporal and smaller spatial scales (Wackermann et al., 1993; Kenet et al., 2003).

Ongoing activity and precision

In free-energy formulations of predictive coding, a major contributor to measured neuronal activity is precision-weighted prediction error. This precision weighting is implemented by increases in synaptic gain (cf. attentional modulation) so that prediction errors are boosted selectively according to the context established by predictions or cues). This means that fluctuating activity levels may reflect not just itinerant optimization of predictions but fluctuations in their precision. Evidence for this interpretation of ongoing activity fluctuations (as a modulation in precision or gain afforded to afferent information) comes from investigations of false vs. correct perceptual inference. Intrinsic brain activity (as indexed by fMRI signal) could be interpreted as a correlate of sensory evidence in random walk or race models (in essence an extension of signal detection theory over time Smith and Ratcliff, 2004; Gold and Shadlen, 2007) or as a proxy for precision in free-energy formulations of predictive coding (Friston,

2008). Crucially, these two accounts can be tested against findings in threshold detection paradigms discussed above (Hesselmann et al., 2008a; Sadaghiani et al., 2009). The former (evidence accumulation) framework suggests high pre-stimulus activity (i.e., a high starting level for the random walk) will bias towards subsequent stimulus detection (true hits or false alarms). Conversely, the latter (predictive coding) framework suggests that high ongoing activity (i.e., precise prediction errors) will bias towards subsequently correct inference (hits or correct rejections). In two independent datasets, we recently found that pre-stimulus activity levels were associated with the latter perceptual outcome and hence support the interpretation of ongoing activity as reflecting the precision of perceptual inference (Hesselmann et al., 2010) (**Figure 5**).

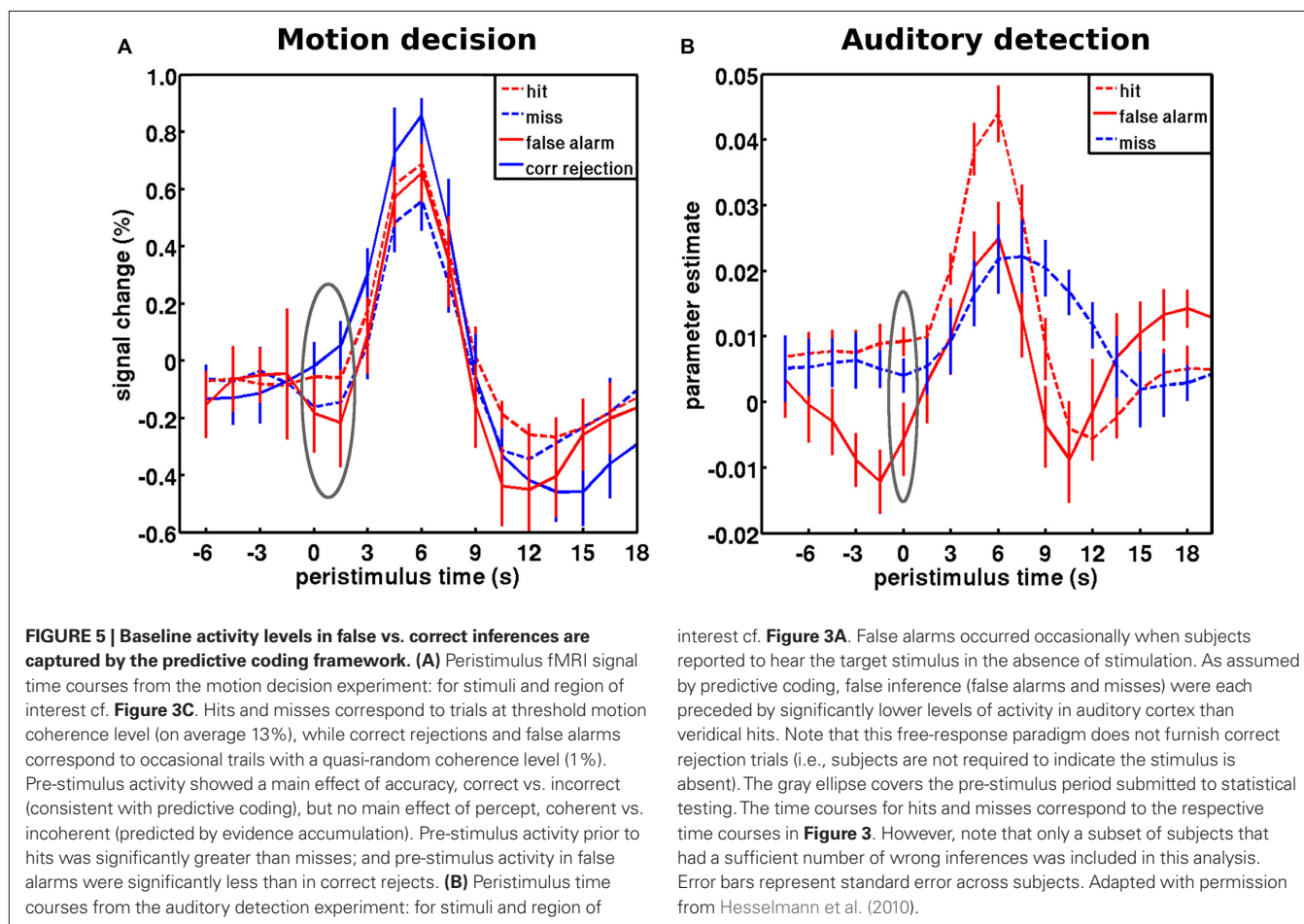
The implementation of precision in the predictive coding framework is necessitated by the presence of noise in environmental states or sensory input and plays a key role in regulating the reliability or relative weighting of bottom-up prediction errors against top-down predictions. Thus, this gain could represent a mechanism that is very suitable for mediating selective attention (Friston, 2009). Of note however, a shared final common neural pathway does not imply that fluctuations in ongoing activity necessarily reflect fluctuations in attention (cf. the discussion of cueing paradigms in the previous section and itinerant optimization of neuronal activity above). In conclusion, the free-energy formulation presents an

attractive theoretical framework for a unified approach to a diversity of neurophysiological observations, including those related to ongoing activity fluctuations.

SUMMARY

In the recent years, intrinsic brain activity has become a new and enticing focus of interest and research into brain function (Fox and Raichle, 2007). In spite of conceptual concerns about studying unconstrained brain activity (Morcom and Fletcher, 2007a,b) studies of intrinsic brain activity during rest as well as in paradigm settings have proven very fruitful in understanding the functional role of ongoing activity and its relation to cognitive processes (Buckner et al., 2008; Greicius, 2008; Hesselmann et al., 2008b; Sadaghiani et al., 2009).

Ongoing activity is organized in a functional architecture at various temporal and spatial scales (Kenet et al., 2003; Bassett et al., 2006; Meunier et al., 2009). It has been established that evoked neural responses are embedded into this underlying functional architecture (Tsodyks et al., 1999) and cannot be fully understood in isolation from the context established by ongoing activity. Therefore, trial-to-trial variability in evoked responses is not just noise but a non-random function of network fluctuations (Fontanini and Katz, 2008). For this reason the current review of ongoing activity considered its spatiotemporal structure in relation to moment-to-moment variability in cognition.



With respect to structure, we emphasized that behaviorally relevant ongoing activity is hierarchically organized and does not seem restricted to clear-cut temporal or spatial scales. The spatial patterns of ICNs and the membership of constituent regions are gradual and display a global-to-local connectivity, reminiscent of small-world topologies (Bullmore and Sporns, 2009). We further discussed that the strength of these correlations is constrained by structural connectivity but is modulated by mental states and current context, strongly suggesting a functional component to intrinsic activity fluctuations (i.e., dynamics on structure).

We have tried to substantiate the role of intrinsic fluctuations in terms of the necessarily itinerant dynamics entailed by internal (generative) models of the world the brain might use to make predictions about its sensorium. In doing this, we hoped to establish a formal link between the notion of mind wandering and itinerancy (wandering dynamics) in computational accounts of perceptual learning and inference. Furthermore, we extended this account to include the modulation of prediction error signals by their precision and suggested that measured fluctuations in neuronal activity may reflect modulations in synaptic gain; of the sort seen in fast synchronized neuronal exchanges and attentional modulation.

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ACKNOWLEDGMENTS

S. Sadaghiani is supported by the Friedrich-Ebert Foundation (Germany). G. Hesselmann is supported by a Minerva fellowship (Max Planck Society). Our research is funded by the Agence Nationale de la Recherche (SPONTACT grant), France.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 05 February 2010; paper pending published: 07 March 2010; accepted: 12 May 2010; published online: 23 June 2010.

Citation: Sadaghiani S, Hesselmann G, Friston KJ and Kleinschmidt A (2010) The relation of ongoing brain activity, evoked neural responses, and cognition. *Front. Syst. Neurosci.* 4:20. doi: 10.3389/fnsys.2010.00020

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