The Impact of Ongoing Brain Activity on the Variability of Human Brain Function and Behaviour

Dissertation

zur Erlangung des Grades eines Doktors
der Naturwissenschaften

der Fakultät für Biologie
und
der Medizinischen Fakultät
der Eberhard-Karls-Universität Tübingen

vorgelegt
von

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aus Mashhad, Iran

Mai 2010

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Tag der mündlichen Prüfung: 27.07.2010

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"Rest Energy" by Marina Abramovic, 1980.

The fascination of this performance by Abramovic lies in the energy that emanates from a state of apparent rest. It described rest as a sensitive state of balance suspended at high energetic cost. The brain's "resting" state is likewise a state of very high energy expenditure. The overwhelming majority of the extremely costly brain activity is indeed intrinsic and makes the observer marvel about function of such complex state of spatio-temporal organization. Beyond of what can be captured by this analogy is the dynamic character of intrinsic brain activity that is central to the provided work.

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Contents

1 Synopsis

1.1 Introduction to ongoing brain activity

Ongoing brain activity has been observed since the earliest neurophysiological recordings in humans (for instance Berger, 1929). Nonetheless, brain research has long under-investigated this aspect of the brain's design and thus its functional importance has remained mostly elusive. Ongoing activity refers to neural activity that is intrinsic to the brain, i.e. not driven by any specific external stimulus. In the recent years, this intrinsic brain activity has become a new focus of interest and research (Fox and Raichle, 2007; Buckner et al., 2008; Raichle, 2009). Three types of observations have substantially contributed to this rise in interest. First, the brain expresses high levels of spontaneous activity during a wide range of states even in the absence of external stimulation or overt behaviour. Second, this intrinsic brain activity undergoes large spontaneous modulations that occur coherently across reproducible large-scale and spatially-distributed networks. And third, ongoing brain activity impacts on evoked information processing and hence ultimately on perception and behaviour.

Ongoing brain activity constitutes a major proportion of neural activity with stimulus- or task-evoked responses representing a relatively small addition (Arieli et al., 1995; Fiser et al., 2004). The neuroimaging work by Raichle and colleagues on activity and energy expenditure in the resting awake brain further underlines these findings (Raichle et al., 2001). During task-free resting state, the oxygen metabolism as measured by Positron Emission Tomography is very high throughout the cortex. In fact, task-related increases in neural metabolism are quite small ($< 5\%$) when compared with the large resting consumption (Raichle and Mintun, 2006). One aspect of brain activity during unconstrained resting wakefulness has been particularly intensely discussed in the recent years. A group of brain regions including ventromedial prefrontal cortex (mPFC), lateral parietal cortex and especially precuneus/posterior cingulate cortex (PCC) show particularly high resting metabolism as measured by blood flow and oxygen consumption ($CMRO_2$) in comparison with the rest of cortex (Raichle et al., 2001). This group of regions, dubbed the "default mode" network, decreases activity during extroverted processing as compared to rest (Gusnard and Raichle, 2001). These task-induced decreases occur in the same regions independent of the type of task and correlate with the degree of functional challenge (McKiernan et al., 2003; Greicius and Menon, 2004; Mason et al., 2007; Singh and Fawcett, 2008). These observations together with the role of PCC in mnemonic processes (Fletcher et al., 1995; Shannon and Buckner, 2004; Daselaar et al., 2009) and mPFC in self-referential processes (Binder et al., 1999) have led to the (controversial) proposal that activity in this network is related to conscious, yet experimentally uncontrolled mentation (McGuire et al., 1996; Buckner and Carroll, 2007; Mason et al., 2007). The default mode network is referred to as the "task-negative" network (Gusnard and Raichle, 2001), contrasting it with the "task-positive" behaviour of regions such as dorsolateral parietal, frontal and prefrontal areas commonly increasing activation in response to cognitive tasks (Corbetta et al., 2002; Smith et al., 2009).

Intrinsic activity not only constitutes a substantial part of brain activity but also exhibits remarkably large spontaneous modulations that can surpass task-evoked responses in amplitude (Arieli et al., 1995). These fluctuations are found over a wide range of temporal and spatial scales. Intrinsic activity is temporo-spatially organized, replaying for instance functional architecture. As an example, distinct orientation-encoding populations within orientation maps of visual cortex spontaneously increase activity in alternating manner at sub-second speed (Tsodyks et al., 1999; Kenet et al., 2003). Whole-brain Blood-Oxygenation-Level-Dependent signal (BOLD) imaging has revealed spatio-temporal structure of ongoing brain activity at the scale of distributed networks, substantially contributing to the recent strong interest in this subject (Fox and Raichle, 2007). The first report of coherent spontaneous activity fluctuations within organized spatial patterns involved the motor system (Biswal et al., 1995). Several such intrinsic functional connectivity networks (ICNs)[1] have since been observed (see Figure 1) (Lowe et al., 1998; Greicius et al., 2003; Laufs et al., 2003; Beckmann et al., 2005; Damoiseaux et al., 2006; Varoquaux, Sadaghiani et al., 2010). These networks, whose regions undergo coherent spontaneous activity fluctuations, strongly resemble patterns of activation or deactivation evoked in task contexts (Smith et al., 2009). They include different sensory systems (e.g. Nir et al., 2006), the default mode network (Greicius et al., 2003; Fox et al., 2005; Fransson, 2005) and several task-positive attentional and cognitive control networks (Fox et al., 2006; Dosenbach et al., 2007; Seeley et al., 2007; Vincent et al., 2008).

Despite the static impression imposed by ICN maps as a result of correlation analyses, it should be noted that the correlative relationship between constituent regions of ICNs is not rigid, but rather these regions decrease and increase activity in coherence with each other more often than with other regions (Chang and Glover, 2010; Popa et al., 2009). This fact inevitably results in difficulties in drawing distinctive boundaries between networks and assigning certain brain areas to particular ICNs. Another characteristic that has likely led to more prevalent difficulties regarding the anatomical definition of ICNs and caused much confusion[2] is the nested correlation structure of ongoing brain activity. This structure should be thought of as a hierarchical organization of multiple, spatially embedded levels of correlation, ranging from global grey matter correlation across the entire cortex to within-region correlations (for detailed discussion see section 2.5). Consequently, the spatial pattern and number of constituent regions depends upon the emphasis and specific methods of each laboratory, such as exact positioning of the

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[1] Intrinsic functional connectivity networks are also commonly referred to as resting-state functional connectivity (rs-fc) networks, resting state networks (RSNs) or functional connectivity MRI (fcMRI) networks. However, they should not be conceptually restricted to certain mental states nor imaging methods.

[2] For instance, cf. controversy (stemming from global grey matter correlations) regarding putative ”anti-correlation” between the default-mode network and certain task-positive regions in Fox et al. (2009) vs. Murphy et al. (2009). Another example concerns the definition of one large task-positive system (Fox et al. 2005; Golland et al., 2008) versus different numbers of segregated task-positive networks (Fox et al., 2006; Dosenbach et al., 2007; Seeley et al., 2007; Vincent et al., 2008). One aspect of this discrepancy is discussed in section 1.2.

correlation seed in seed-based approaches and the model-order chosen in independent component analyses (ICAs). We have proposed an automatic model-order selection as a solution to the latter problem (Figure 1, Varoquaux, Sadaghiani et al., 2010).

The spatio-temporal ICN patterns persist across different states, from task- and stimulus-induced active states (Fair et al., 2007a; Golland et al., 2007; Eckert et al., 2009), over resting wakefulness (Greicius et al., 2003; Fox et al., 2005; Fransson, 2005), light and deep sleep (Horovitz et al., 2007; Horovitz et al., 2009) and light sedation (Greicius et al., 2008), all the way down to the complete absence of awareness in deep anaesthesia in monkeys (Vincent et al., 2007) or in vegetative state patients (Boly et al., 2009). However, although qualitatively stable, ICNs show quantitatively fine-grained changes in correlation strength both at short time scales in response to immediate task-demands (Waites et al., 2005; Albert et al., 2009; Hasson et al., 2009; Tambini et al., 2010), through the circadian time scale of the sleep-wake cycle (Horovitz et al., 2007; Horovitz et al., 2009), as well as longer time scales reflecting intense learning (Lewis et al., 2009). Interestingly, intrinsic functional connectivity strength is altered between selective regions in many psychiatric or neurodegenerative disorders (e.g. He et al., 2007; Seeley et al., 2009) and shows a gradual decline with the pathological loss of consciousness from healthy state to minimally conscious state, vegetative state and ultimately coma (Vanhaudenhuyse et al., 2010). Intrinsic connectivity analysis thus promises to become a marker of normal brain function (Greicius, 2008). But the importance of ongoing brain activity becomes most evident in its impact on moment-to-moment evoked information processing.

> ”Ignoring brain-derived variability would be a great loss since this spontaneous coordinated variability may be the essence of cognition.” – György Buzsáki (2006)

Stimulus- or paradigm-evoked brain responses to repeated identical stimuli show high variability from trial to trial for instance in amplitude, a phenomenon observed across the temporal and spatial scale of electrophysiology, optical and functional imaging methods (Schiller et al., 1976; Tsodyks et al., 1999; Ress et al., 2000; Pessoa and Padmala, 2005). The influential work of Arieli and colleagues showed that this evoked-response variability is largely accounted for by spontaneously occurring fluctuations of ongoing activity (Arieli et al, 1996). They investigated background and stimulus-evoked activity with concurrent optical and electrophysiological methods in anaesthetized animals. By linearly adding an average evoked response estimate to the initial state of ongoing activity at stimulus onset of a given trial they could predict the veridical evoked activity pattern in that trial with high precision. Fox et al. (2006a) made a similar observation at very different spatial and temporal resolution using fMRI. In a finger-tapping paradigm, they used the motor cortex contralateral to the task-relevant hemisphere as a measure of ongoing activity fluctuations, taking advantage of the coherence of these fluctuations across the motor ICN. They found that trail-to-trial variability of finger movement-evoked activity in motor cortex could be largely accounted for by ongoing activity fluctuations measured in the contralateral motor cortex.

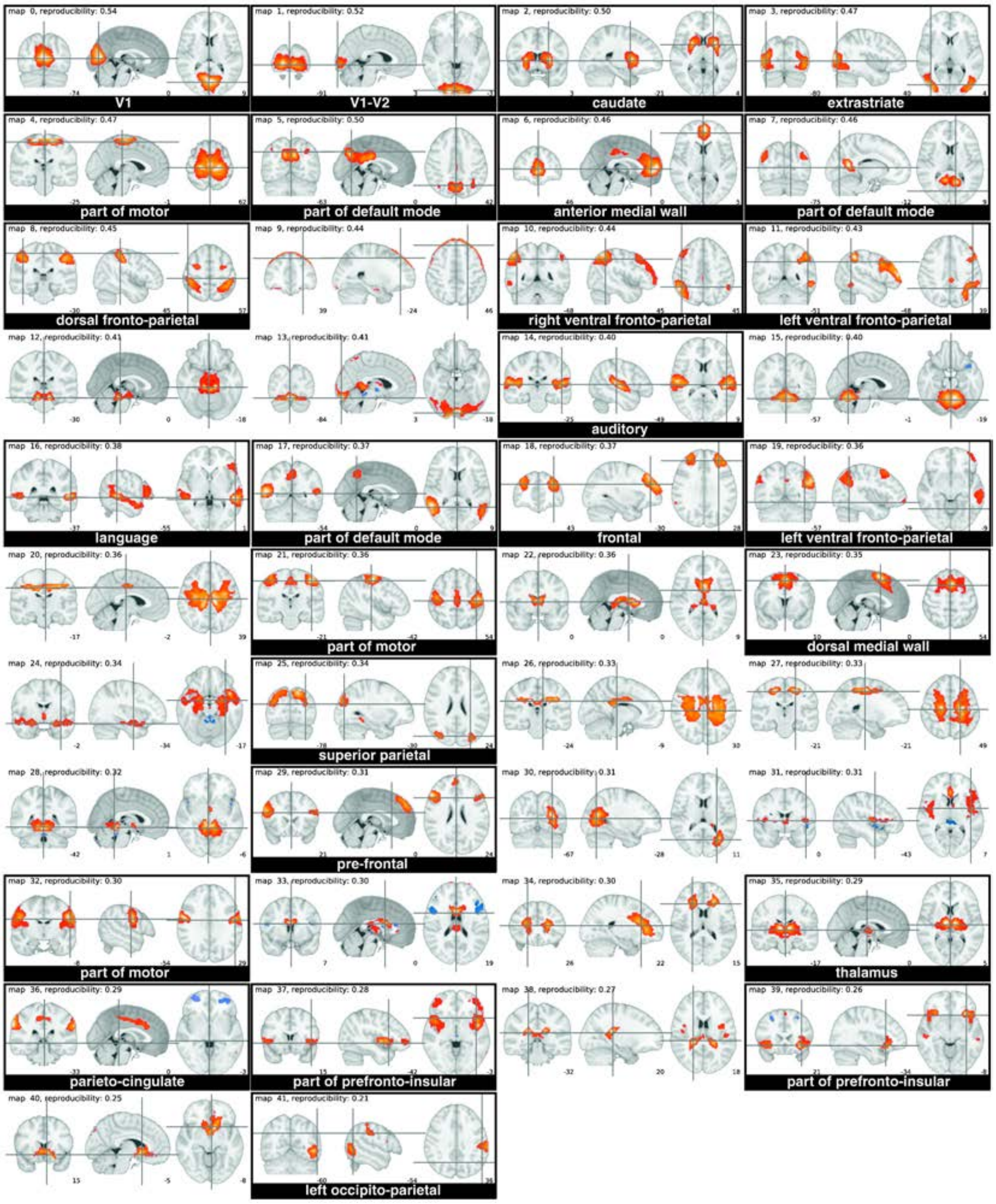

Figure 1: **ICN maps extracted by ICA from a resting-state data-set.** We introduced and applied an estimation procedure (CanICA) that uses a hierarchical model for patterns in multi-subject fMRI datasets, similar to mixed-effect group models used in linear-model-based analysis (Varoquaux, Sadaghiani et al. 2010). The maps are ordered by reproducibility across subjects. Maps corresponding to functionally plausible intrinsic connectivity networks (ICNs) are in a black frame, whereas maps likely corresponding to artefacts are not framed. Extracted brain networks are labelled with the name of the general structure to which they can be related. The right hemisphere is on the left.

Crucially, these ongoing activity fluctuations that propagate into the induced response were shown to translate into behavioural variability. A follow-up to the aforementioned study by Fox et al. showed that trial-by-trial variability in task-evoked motor cortex activation affected the spontaneously variable force that subjects applied in different trials when pressing a response button (Fox et al., 2007). Instead of using simultaneously recorded signal in a region that belongs to the same ICN but is silent in a task context, previous studies from our laboratory have taken pre-stimulus signal in the same region that will subsequently respond to a given stimulus as a measure of ongoing activity. In a decision task on Rubin's vase-faces ambiguous figure with brief stimulus-presentation at long variable intervals of ≥ 20 s, subjects reported perception of faces on approximately half of the trials and a vase on the other trials (Hesselmann 2008b). Higher pre-stimulus activity levels in the right fusiform face area (FFA), a region specialized on face processing, were found to bias towards the percept of faces rather than a vase. This finding was shown to generalize to the domain of visual motion perception (Hesselmann et al. 2008a). In a decision task using random dot kinematograms at individual threshold motion coherence level, subjects indicated whether they saw coherent or random motion on a given trail. This time, subjects' perceptual decision was biased by pre-stimulus activity levels in right middle temporal cortex (hMT+). Perception of coherent motion was preceded by significantly higher ongoing activity in this motion-sensitive region. Likewise, Boly et al. (2007) investigated the perceptual impact of pre-stimulus activity fluctuations in a somatosensory detection task. For laser stimuli close to perceptual threshold, pre-stimulus activity levels in large distributed systems resembling ICNs biased whether or not a stimulus was perceived on a given trial. The system biasing towards perceiving the stimulus comprised task-positive systems of parietal, frontal and prefrontal areas. Conversely, on trials where subjects missed the threshold stimulus, pre-stimulus activity levels were higher in the task-negative default-mode network. In summary, intrinsic activity fluctuations influence perceptual and behavioural outcome. The need for investigating what aspects determine sign and site of this influence have motivated my first experiment (section 2.2).

Electro- (EEG) and magnetoencephalographic (MEG) studies have likewise shown the impact of ongoing activity on subsequent processing and behaviour by investigating pre-stimulus band-limited oscillation power and phase[3]. 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). 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 in a go no-go task that false alarms were preceded by higher levels of α band power in the occipital cortex and bilateral somatosensory cortices

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[3] Only un-cued settings are discussed here. Several studies have shown the impact of preceding oscillation power levels but in spatially cued settings (e.g. Thut et al. 2006, Wyart and Tallon-Baudry, 2009) where the pre-stimulus power levels could be thought to reflect variability in cue-induced evoked response amplitude rather than spontaneous fluctuations. For a detailed comparison with cued settings see section 2.5.

(μ rhythm) as compared to correct withholds on no-go trials (Mazaheri et al., 2009). Palva and colleagues investigated pre-stimulus power fluctuations with full-band EEG sensitive to infraslow fluctuations (<0.1 Hz) using a somatosensory threshold detection task in 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 sensorymotor cortex, and with highest power of these bands over parietal electrodes (Linkenkaer-Hansen et al., 2004). Interestingly, in this task setting the phase of infraslow 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). Invasive electrophysiological methods have been used to characterize these infraslow fluctuations, their relation to oscillatory activity and to the spatial structure of infraslow activity fluctuations as measured with fMRI. In anesthetized monkey primary visual cortex, fMRI signal fluctuations strongly correlate with simultaneously measured infraslow band-limited LFP power fluctuations, multi-unit activity and spiking rate of small neuronal groups (Shmuel and Leopold, 2008). In presurgical human patients, infraslow fluctuations have been observed in band-limited LFP power and spiking rates (depth electrodes) and shown to be correlated across selective, functionally related electrodes as measured by electrocorticograpgy (ECoG) (Nir et al., 2008). He et al. (2008) showed that slow cortical potentials (<0.5 Hz) as measured by full-band ECoG over sensory-motor areas in fact express a spatial cross-electrode correlation pattern very similar to that measured by fMRI intrinsic connectivity in the same patients. The relation of fluctuations in network-confined activity levels, in oscillation power and in spontaneous top-down cognitive control motivated my simultaneous EEG-fMRI study (section 2.3).

1.2 Summary of presented work on the functional impact of ongoing brain activity

Sign and anatomical site of the impact of endogenous activity onto behavioural outcome is an open matter of current research. The spatial pattern within which ongoing activity affects perception and behaviour can range from very focal variations, e.g., in highly specialized sensory regions (Hesselmann et al., 2008b; Hesselmann et al., 2008a), to effects from large-scale systems (Boly et al., 2007; Fox et al., 2007). What determines the spatial pattern within which this functional impact occurs, and whether higher baseline activity levels in a given region or system facilitate or deteriorate perceptual performance?

In the aforementioned study by Boly et al. (2007) somatosensory detection was facilitated by higher pre-stimulus activity levels in task-positive regions, notably the thalamus, dorsal anterior cingulate cortex (dACC) and anterior insula (cf. later discussion of the alertness network), as well as parietal and frontal areas including intra-parietal sulcus (IPS) and dorso-lateral prefrontal cortex (dlPFC). Conversely, higher baseline activity in the task-negative default-mode network impaired subsequent detection performance. A related observation regarding the deteriorating influence of activity levels in the default-mode network comes form studies that have directly targeted the neurobiological basis of erroneous behaviour (Li et al., 2007; Eichele et al., 2008). Rather than investigating baseline fluctuations, these studies related trial-by-trial performance to variability in evoked responses to the immediately preceding trial. They found that higher evoked response amplitudes in default-mode network regions degrade motor performance in speeded motor control tasks.

These observations together with the typical task-induced activation vs. deactivation of these systems could motivate a dichotomic view in which higher ongoing activity in task-positive brain networks would facilitate performance whereas higher activity levels in the default mode network would degrade performance (Golland et al., 2008). From a computational point of view, however, such a simplistic account seems unlikely. As discussed above, neural processing of stimulus-evoked information is a function of local and distributed neural networks in which it is embedded (Fontanini and Katz, 2008), and therefore in all likelihood is subject to the moment-to-moment state of the respective network at each level of processing hierarchy. Which network is exerting an influence, and whether it is facilitating or detrimental, would then depend on the functional role of that network in the specific task at hand. We hypothesized that the cognitive context determines where in the brain an impact will occur, and whether it will be deteriorating or facilitatory.

Extending previous work in the visual modality from our laboratory discussed above (Hesselmann et al. 2008a, b) we probed the aural consequences of baseline variations in an auditory detection paradigm using a very sparse event-related fMRI design (section 2.2, Sadaghiani et al., 2009). In contrast to those former studies, here we targeted distributed effects with an emphasis on the perceptual impact of large-scale ICNs. Therefore, rather than a decision task, we chose a threshold detection paradigm, which previously was found to invoke large-scale effects in the somatosensroy modality (Boly et al., 2007). We moved to the as yet unassessed auditory modality and adopted a context that was different from previous studies in the sense that the stimulus comprised little spatial connotation (as compared to visual and somatosensory modalities) and was presented in a free-response setting. Subjects listened for a broad-band noise target sound that was presented at unpredictable intervals of 20-40 s and at an individually-defined detection threshold against scanner background noise. They freely pressed a button whenever they perceived the target.

Successful detection was preceded by significantly higher pre-stimulus activity in early auditory cortex as compared to misses. We could thus generalize earlier findings with respect to local effects in specialized sensory areas (Hesselmann et al., 2008a; 2008b) to an as yet not studied modality. This study involved detection of near-threshold stimuli in a free-response setting instead of two-alternative forced-choice decisions on ambiguous but clearly notable stimulation as in the earlier work. As we expected the effects extended beyond the relevant sensory region and into three large-scale ICNs. Increased perceptual performance was associated with higher pre-stimulus activity in a network comprising thalamus, anterior insula and dACC. We proposed that this finding suggests a role for this ICN in maintenance of alertness and pursued this hypothesis directly in a subsequent study (see below and section 2.3). Likewise, higher baseline activity in the precuneus/PCC region of the default mode network preceded hits, a finding that at first glance might appear at odds with the existing literature but that likely 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). In accord with this view, this default mode network region was task-positive in this experiment and showed task-induced activation before entering a delayed deactivation. Again, counter to common intuition higher baseline activity in the dorsal attention ICN including parietal and frontal areas biased towards misses. This finding presumably reflects the absence of a spatial component in our paradigm in which non-spatial attentional operations might compete with the processing of spatial information by the dorsal attention system for similar central resources.

We concluded that the simplistic account is hence insufficient. Rather, the effects of spontaneous baseline activity fluctuations on perception depend upon the specific context in which stimuli are embedded and, in parallel the specific states of the relevant brain systems in processing the incoming sensory information. In our case, with an essentially non-spatial, novel and non-semantic stimulus we could unveil different and in fact opposite contributions from ongoing activity than in the existing previous studies. An additional important finding concerns the aforementioned task-positive attentional and cognitive control networks. These putative networks are co-activated in most paradigm settings (e.g. Shulman et al., 2003; Wu et al., 2007) and their ongoing activity has been associated with uniform functional and behavioral impacts (Boly et al., 2007). Anatomical segregation on the basis of intrinsic functional connectivity as well as functional characterization of these systems is still a matter of open debate (for a discussion cf. section 2.5). Despite a certain level of shared ongoing activity variance (Fox et al., 2005), we provide evidence for functionally independent and antagonistic influences on perceptual performance of two task-positive systems often described as conjoint, i.e. deterioration by the parieto-frontal dorsal attention ICN, and facilitation by a cingulo-insular-thalamic ICN. While the former is well-characterized to implement selective spatial attention (Corbetta and Shulman, 2002), functional characterization of the latter has remained elusive.

This cingulo-insular-thalamic network has received diverse functional labels in other studies. While some investigators have defined one large ICN for cognitive control (Vincent et al., 2008), others have attempted to dissect this system into sub-networks linked to (1) executive and adaptive control and (2) task-set maintenance or salience (Dosenbach et al., 2006; Dosenbach et al., 2007; Seeley et al., 2007). Our paradigm required the simple detection of non-semantic sparse stimuli through the maintenance of tonic alertness and hence did not support the above functional characterizations. Results from our previous study suggest the hypothesis that this cingulo-insular-thalamic network is involved in the maintenance of tonic or sustained alertness. In accord with this interpretation, several studies that explicitly probed tonic alertness found effects in similar brain structures (Sturm and Willmes, 2001; Sturm et al., 2004). In my second experiment, I sought to further corroborate this functional interpretation (section 2.3, Sadaghiani et al., 2010a).

Due to the conceptual impact of frameworks that emphasize cue-driven attentional functions (Posner et al., 1980), tonic alertness has remained somewhat under-studied in functional neuroimaging experiments. But an analogous EEG literature suggests that sustained alpha oscillations are the most prominent signature of tonic alertness (Makeig and Jung, 1995; Jung et al., 1997). If our functional interpretation was correct, activity fluctuations (as measured by fMRI) within this ICN in the absence of any paradigm should be associated with fluctuations in the electrical signatures of tonic alertness (as recorded by concurrent EEG) and hence show a positive correlation with alpha band power. In this study, we used a fairly recent methodological approach, concurrent EEG and fMRI recording of ongoing (i.e. continuous and task-unconstrained) human brain activity, to test this hypothesis.

Previous concurrent EEG-fMRI studies have linked power fluctuations in EEG frequency bands to activity in ICNs. However, not even the most comprehensive of these studies included the cingulo-insular-thalamic ICN (Mantini et al., 2007). And regarding alpha oscillations as the most salient feature of the EEG during resting wakefulness, previous findings involved mainly negative correlations (Goldman et al., 2002; Laufs et al., 2003; Moosmann et al., 2003). We reinvestigated the issue of positive correlation with alpha power by means of two analyses of concurrent resting-state EEG-fMRI. In a first region-of-interest approach, we regressed the BOLD time course extracted from the cingulo-insular-thalamic ICN onto the spectrally resolved EEG power fluctuations. This analysis allowed us to identify the putative frequency bands to which this ICN is linked. Second, we performed a voxel-wise regression of the BOLD data with a band-limited global field power time course of alpha to identify brain areas whose activity is correlated with power within this band. In line with previous literature that emphasizes specifically upper alpha in (inhibitory) cognitive control, we concentrated the latter analysis on this band as defined subject-by-subject relative to individual alpha power peak (Klimesch, 1999).

As hypothesized, we found selective correspondence between global power in the alpha band and activity in the system we termed the "tonic alertness network". The channel-frequency spectrum revealed positive correlations with the BOLD time course extracted from the tonic alertness ICN. These correlations occurred selectively in upper alpha (∼10-12 Hz) and broad beta (∼17-24 Hz) bands; the latter is in line with the previously observed relationship between beta power and sustained performance levels (Townsend and Johnson, 1979; Belyavin and Wright, 1987). The correlations occurred globally across the majority of EEG-channels resulting in a distributed topography. We observed a similar spectral pattern in all individual constituent regions of the network. In the voxel-wise analysis, positive correlations of upper-alpha global field power with the BOLD signal occurred selectively in regions of the tonic alertness network comprising dACC, anterior insula, thalamus and anterior prefrontal cortex. Negative correlations with upper alpha power were observed in extra-foveal visual areas and the dorsal attention network. An equivalent analysis for the beta band revealed more confined correlation with dACC and thalamic-basal sub-cortical regions.

We sought to corroborate our functional interpretation of the tonic alertness network in our earlier auditory detection dataset. We used the network defined through positive correlation with alpha power as a spatial mask to extract peri-stimulus time courses of the previous activation study. We hypothesized that if the system as defined here by EEG correlation underpinned tonic alertness then it should show the same pre-stimulus effects as previously found for the cingulo-insular-thalamic ICN. Indeed, successful detection of the auditory stimulus as compared to misses was preceded by significantly higher pre-stimulus activity levels in those areas where activity correlates with upper alpha band power in a different set of subjects.

In summary, we observed in a large subject sample that ongoing activity in an intrinsic connectivity network comprising anterior insula, dACC, anterior prefrontal cortex and thalamus was tied to global field power in the upper alpha range. While previous exploratory studies found pieces of this network to correlate with (mostly occipital) alpha (Goldman et al., 2002; Moosmann et al., 2003; de Munck et al., 2007; Ben-Simon et al., 2008; Difrancesco et al., 2008), this is the first demonstration linking a specific frequency component with a widespread topography to an entire intrinsic connectivity network. Of note, this network did not include other task-positive regions such as dlPFC or lateral parietal cortex and thus supports the view of segregated cognitive control networks (Dosenbach et al., 2007; Seeley et al., 2007). We've outlined our hypothesized functional role of this network but also proposed a hierarchical view of attentional functions in which alertness and selective attention deploy antagonistic but mutually reinforcing mechanisms that manifest in the power of alpha oscillations. Specifically, we propose that the cingulo-insular-thalamic network serves the maintenance of tonic alertness through synchronized oscillations in the upper alpha range that generalize over major portions of the cortex. Selective attention, likely mediated by activity in the dorsal attention network, focally disrupts alertness-related suppression in accordance with the type of input expected and hence manifests as local attenuation of alpha activity (see section 1.3 for further discussion).

In our two studies introduced above I argued that ongoing brain activity fluctuations are source of variability in behaviour, ranging from simple perceptual decisions up to higher cognitive functions such as maintaining alertness. Variability in function could be potentially detrimental to overall performance. So why doesn't the brain compensate for this background "noise"? To answer this question we need to further understand the very nature of intrinsic brain activity.

We have proposed that spontaneous brain activity reflects the brain's internal model of the environment, i.e., the neuronal activity that predicts the causes of sensory inputs (section 2.5 part 4, Sadaghiani et al. 2010b). The notion that ongoing activity represents the brain's internal context for processing external stimuli has recently been emphasized by many researchers based on the observation that background activity modulates stimulus-evoked responses (Kenet et al., 2003; Buzsáki, 2006; Fontanini and Katz, 2008). One theoretical account that is particularly well-suited to aid in the formalization of this interaction of internal and external information is provided by a Bayesian view of the brain as hierarchical cortical inference machine (Kersten et al., 2004; Hohwy et al., 2008). In such a view, perception is a recognition mechanism that substantially depends on the internal model that generates predictions on sensory input.

This predictive nature of perceptual processes is formally embedded into the broader context of a free-energy account of brain function by Karl Friston (2009; 2010). The free-energy principle states that the brain's perceptual system seeks to minimize surprise. This is achieved by continuously updating an internal model that emits top-down predictions of sensory input. Unexpected sensory input that cannot be "explained away" by the current internal model leads to the signalling of bottom-up prediction errors (predictive coding). Perception rests on the top-down prediction that best succeeds in explaining the bottom-up prediction error caused by incoming sensory information (Friston et al., 2006; Friston, 2009; Friston, 2010). We discuss that within the free-energy framework spontaneous activity becomes a historically informed internal model of causal dynamics in the world that serves to generate predictions of future sensory input. This fits nicely with a large body of experimental observations that support a functional role for itinerant activity in short term (Bick and Rabinovich, 2009) and especially long term memory (Jeffery, 2004; Foster and Wilson, 2006; Vyazovskiy et al., 2008; Diekelmann and Born, 2010). Itinerant fluctuations of this ongoing 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. Importantly, from this view it follows that this itinerant activity also manifests in the absence of sensory information.

However, the free energy framework provides more fine-grained predictions about the nature of intrinsic brain activity. In free energy formulations of predictive coding, a major contributor to measured neuronal activity is *precision-weighted* prediction error. The formulation of precision in this framework is necessitated in order to account for noise in environmental states or sensory input. Precision (inverse variance) regulates the reliability or relative weighting of bottom-up prediction error against top-down predictions (Friston, 2008). Neurophysiologically, precision is thought to be implemented as synaptic gain of prediction error-coding neurons, controlled e.g. through modulatory neurotransmitters (Friston, 2010). In this view, 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. In other words, precision implements selective boosting of itinerant system memories that make up the internal model (section 2.5 Sadaghiani et al. 2010b).

Section 2.4 provides supporting evidence for this interpretation (Sadaghiani, Hesselmann et al. 2010). In short, the nature of intrinsic brain activity in sensory cortex could be interpreted as endogenous implementation of precision in the predictive coding or free-energy framework (Friston, 2008). In the context of perceptual decisions, an alternative hypothesis on the nature of ongoing activity in sensory areas comes from random walk or race models (an extension of signal detection theory (Smith and Ratcliff, 2004; Gold and Shadlen, 2007). In these frameworks, accurate modelling of variability in perceptual decisions requires the implementation of random variability not only in the accumulation process but also independently in the initial pre-stimulus state (Ratcliff, 2001). Consequently, in random walk models intrinsic activity levels in sensory cortex implement the initial level of sensory evidence. In these evidence accumulation models, activity increases with the evidence for a stimulus. Thus, high ongoing activity will bias towards perceiving a stimulus, be it physically present (hit) or not (false alarm). Conversely, under predictive coding, ongoing activity levels in sensory cortex reflect precision of prediction error units that is amplified when sensory noise is low and suppressed when sensory noise is high. Therefore, importantly, while this latter framework suggests that high ongoing activity (i.e., precise prediction errors) will bias towards subsequent correct inference (hits or correct rejections) evidence accumulation models suggest high pre-stimulus ongoing activity (i.e. high starting level of random walk) to bias towards subsequent stimulus detection (true hits or false alarms).

We tested these two possibilities against findings in our auditory threshold detection paradigm discussed above (Section 2.2, Sadaghiani et al., 2009) in which subjects had occasionally reported false alarms in the absence of stimulation. As predicted by the predictive coding account (but incompatible with evidence accumulation models), false inference, i.e. misses and false alarms, where both preceded by significantly lower activity levels as compared to correct inference, i.e. hits. Likewise, we investigated data from the visual motion decision paradigm introduced in the first section (Hesselmann et al., 2008a). In this experiment, both false alarms and correct rejections had been recorded in response to a quasi-random motion stimulus that was occasionally presented as control to the threshold motion stimuli. Again, wrong inference, i.e. misses and false alarms, were foreshadowed by significantly lower ongoing activity levels than both hits and correct rejections. In summary, in both datasets we found that pre-stimulus activity levels biased towards correct inference and hence support the interpretation of ongoing activity -at least as it translates into the fMRI signal- as precision of prediction error signals (section 2.4, Sadaghiani, Hesselmann et al. 2010). In conclusion, our study gave specific insight into the nature of ongoing activity. Importantly however, the implications of this study went beyond this specific question and made use of pre-stimulus activity in sensory cortices to adjudicate two general theories on cortical processing architecture, predictive coding vs. evidence accumulation, which cannot be easily dissociated when investigating evoked activity *per se*.

The above and other aspects that I regard important in understanding the functional significance of spontaneous brain activity have been discussed in our review article (section 2.5, Sadaghiani et al. 2010b).

1.3 Future directions

One future direction of investigation involves the context-dependent dynamics of intrinsic functional connectivity. As discussed above, intrinsic connectivity is subject to quantitative changes, and revealing determinants of these dynamic adjustments is key in understanding the nature and function of fluctuations in ongoing activity. In the context of our auditory detection experiment (Sadaghiani et al., 2009) I have acquired additional scanning sessions within the same subjects. Across sessions, I manipulated the context along with the factors task (i.e. with detection task or passive listening) and perceptibility (stimulus at threshold or largely above threshold volume). I will apply *integration*, a connectivity measure that allows for quantification of the correlation strength (or shared information) between multiple regions of an ICN as well as between ICNs (Marrelec et al., 2008). This measure was proposed by Tononi et al. (1994) on the basis of mutual information as defined in information theory frameworks and laid the foundation for the observation of small-world architectures that optimize segregation and integration in functional and anatomical brain connectivity (Sporns et al., 2004). The very long inter-trial intervals (20-40 s) and long sessions (20 min) in the acquired data permit the complete exclusion of all periods of task-evoked activity and the exclusive use of pure baseline epochs in the connectivity analyses, taking advantage of the mathematical independence of integration from the temporal sequence. This allows for studying adjustments of intrinsic connectivity in response to context or task-set *during* task execution rather than in test re-test designs that compare resting state connectivity before and after task manipulation (Waites et al., 2005; Albert et al., 2009; Tambini et al. 2010) and without influence of the evoked activity itself on the connectivity measure (cf. Eckert et al., 2009; Hasson et al., 2009). I hypothesize that information exchange will selectively increase within and between certain ICNs (e.g. auditory cortex, the alertness system and motor cortex), and decrease between certain other regions in response to context. Interestingly, the large dataset involving detection of peri-liminal sounds, which was used in the previous analyses (Sadaghiani et al., 2009, Sadaghiani, Hesselmann et al., 2010), permits the splitting of the inter-trial baseline periods into pre-hit, pre-miss, and pre-false alarm segments and the calculation of integration as a function of subsequent perception. In summary, these future analyses will enable assessing whether and how intrinsic connectivity is subject to immediate changes in response to ongoing sensory and task context, but also how moment-to-moment functional connectivity affects perceptual performance.

Another particularly interesting aspect that calls for further investigation is the functional role that we have postulated for the cingulo-insular-thalamic system which we termed the alertness network. Our findings open several questions both with respect to cognitive functions as well as their variability. The maintenance of endogenous (uncued), sustained alertness appears to not be bound to specific task sets. This is why I restrain from the functional label ”task-set maintenance” postulated for this network in the related and very interesting recent work of the Peterson group (Dosenbach et al., 2006; Dosenbach et al., 2007; Dosenbach et al., 2008; Fair et al., 2007b). In other words, the function of the alertness network is not an engagement in a specific task, but rather a generalized, active disengagement and readiness for processing. This function is recruited more intensely the more the suppression of irrelevant information becomes necessary. At high demands, this mechanism is cognitively effortful and more strongly subject to variability over sustained periods of time (Mackworth, 1968; Makeig and Inlow, 1993).

Thus, it is important to investigate alertness as a fundamental cognitive faculty but also as a specific source of variability in human perception and behaviour.

Tonic alertness has been generally recognized as a central function in attentional control. Given the complexity and multifariousness of attentional functions the need for a taxonomy is clear. The proposed cognitive architectures differ from one another in several respects, but they mostly include a sustained and intrinsic type of attention as a cognitive faculty distinct from phasic attention. In particular, this function has been conceptualized as "*vigilant attention*" by Robertson and Garavan (2004), as "*tonic alerting*" in a taxonomy of *orienting*, tonic and phasic *alerting*, and *executive control* by Posner (2008), and similarly, as "*vigilance*" by Parasuraman (1998) in contradistinction to *selection* and *control*. Dispite conceptual similarities however, these theories differ from our proposal with respect to the anatomical interpretation of alertness; they commonly emphasize (mostly right-hemispheric) dlPFC and lateral parietal cortex, in contrast to our proposal of a cingulo-insular-thalamic implementation. This discrepancy might stem from the aforementioned difficulty of most paradigms in isolating often co-activated systems that implement distinct aspects of attentional control. For example, an imaging study that serves as principal reference to Posner (2008) used cued alerting rather than endogenously maintained alertness (Coull et al., 2000). We turned to the resting state paradigm to test our hypothesis based on the known electroencephalographic markers of alertness without interference from task-induced selective attention mechanisms. The resulting findings led to a hierarchical view that provides both, a neuroanatomical and an antagonistic electrohpysiological distinction between *sustained alertness* and selective *phasic attention* (Figure 2). This model provides concrete predictions that can now be tested in carefully designed cognitive paradigms.

The difficulty of studying sustained alertness in isolation from phasic attention and executive control explains why the former has been under-investigated as compared to the latter aspects which are easier to manipulate experimentally. Therefore, a future challenge lies in designing paradigms that specifically orthogonalize alertness and phasic aspects of attentional control. It has been proposed that particularly good paradigms to assess tonic alertness are those that require *inhibition* of response to rare events during continuous routine behaviour rather than settings that require an explicit response to the rare target (Robertson and Garavan, 2004). The idea that sustained vigilant attention is particularly necessary in settings that require occasional withhold from behaviour is in line with our interpretation of alertness being implemented as inhibitory top-down control through enhancement of alpha oscillations. In this type of paradigms the necessary level of continuous alertness maintenance can be parametrically modulated by manipulating the predictability of the rare withheld target. Orthogonal to this factor, the paradigm is required to parametrically manipulate selective attention to a certain feature such as colour, orientation, location or pitch. With respect to sensory modality, audition and vision provide different advantages. Alertness has often been studied using auditory tasks (Makeig and Inlow, 1993; Jung et al., 1997; Sturm et al., 2004) and our own study in the auditory modality strongly implicated the alertness network (Sadaghiani et al., 2009). Auditory paradigms might be more sensitive to detect effects of alertness

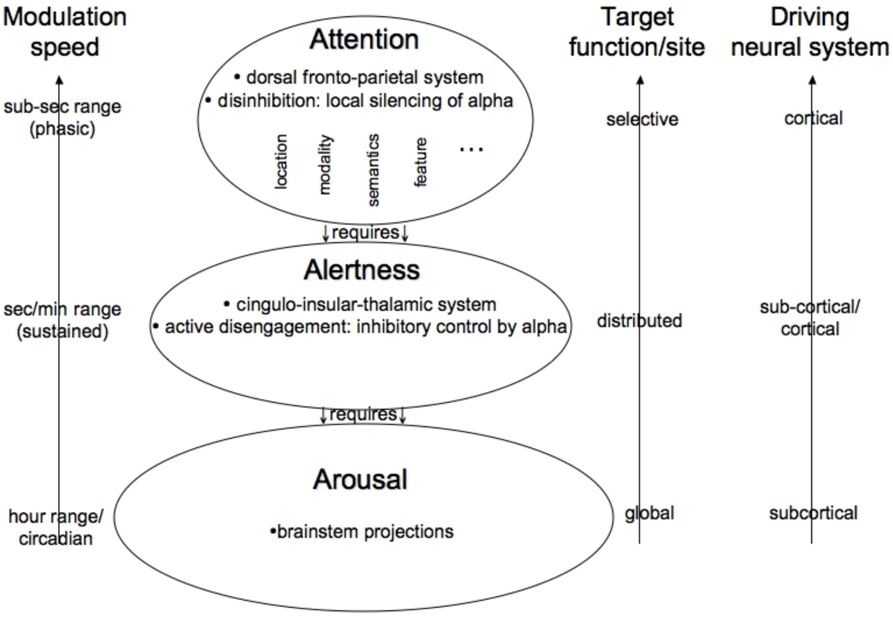

Figure 2: **A hierarchical view on attentional functions**. The distinguishing new characteristic of this proposal is that alertness and selective attention deploy antagonistic but mutually reinforcing mechanisms which manifest with opposite sign in the power of alpha oscillations. Attention, Alertness and Arousal hierarchically depend upon each other but are distinct functions with differing neuroanatomical and mechanistic implementation. Arousal as controlled by the ascending reticular activating system is the basic function of wakefulness and general responsiveness. Building upon this primary level, alertness or vigilance implies top-down controlled readiness for processing and action and, in contrast to phasic attention, is independent of specific content. In our model, this function is put in place by means of rhythmic noise-reduction manifesting in widespread increase of power in the upper alpha band. Note that the cingulo-insular-thalamic network is not the source but a modulator of cortical alpha oscillations. On the contrary, phasic attention acts selectively e.g. upon sensory modality, or stimulus features such as colour and orientation. This function is implemented by fronto-parietal areas, most importantly the superior parietal lobe and frontal eye fields of the dorsal attention system. We have proposed that one mechanism deployed by this network is a selective release from alpha-induced inhibition manifesting in local desynchronization of alpha oscillations. For completeness, it should be noted that this basic model does not depict the likely distinct faculty of adaptive executive control which has been proposed to provide feed-back adjustments of control, and to be driven by a network comprising dlPFC and inferior parietal cortex (Dosenbach et al., 2006). For complimentary discussion see section 2.3, Sadaghiani et al., 2010a.

as they reduce contamination by spatial attention in behavioural, electrohpysiological and functional imaging measures of alertness. For example, alpha oscillations are particularly susceptible to eye movements and spontaneous covert attention shifts in visual paradigms. On the other hand, visual tasks provide unparalleled possibilities for focally guiding and isolating effects of selective attention by making use of the spatially segregated organization of the visual system. Visual attention can be selectively guided to different retinotopically-represented locations, or to dorsal- vs. ventral-stream features such as location vs. identity (Jokisch and Jensen, 2007) or motion direction vs. color (Snyder and Foxe, 2010). Paradigms adjusted to disentangle alertness and selective attention can be used in functional imaging studies to directly investigate our functional interpretation of the cingulo-insuar-thalamic network, and in MEG studies to assess the proposed antagonistic mechanism by which alertness and selective attention deploy alpha oscillations. Additionally, trial-by-trial variability in these cognitive functions can be especially well studied using concurrent EEG-fMRI.

Finally, the mechanism by which alertness acts locally, i.e. alpha-induced inhibition, requires invasive investigations in task settings. In the context of top-down control, alpha oscillations have been conceptualized to entrain local neural populations into a rhythmic suppression (Klimesch et al., 2007), a principle termed "pulsed inhibition" (Mathewson et al., 2009). Examples of cyclic inhibition of intrinsic neural spiking in the alpha frequency range have indeed been observed (Lorincz et al., 2009). However, how such a mechanism might be dynamically engaged in implementing cognitive control functions such as alertness is an open question. While studying the effects of alpha synchronization upon fine-scale local processing requires single and multi-unit recordings in behaving animals, several aspects of alertness on local processing can be studied using ECoG and depth electrodes in pre-surgical epilepsy patients to which I will have access in the near future. These methods allow me to test, with high spatial resolution, the hypothesis that alertness enhances alpha oscillations accompanied by suppression of neural activity, while selective attention leads to focal desynchronization and release from inhibition in local information processing. Another question arises from our observation that activity in the alertness network correlates with the majority of scalp EEG channels. The unobscured signal in ECoG would allow me to verify the distributed character of alertness control that we have proposed. In summary, our neuroanatomical and electrohpysiological hypotheses on sustained alertness maintenance provide a rich repertoire of predictions to be tested in a variety of future studies.

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2 Peer-reviewed publications and manuscripts for cumulative thesis

2.1 Delineation of contribution to collective work

The thesis includes four peer-reviewed papers corresponding to sections 2.2 to 2.5. In the following I specify the contribution of each of the co-authors and myself.

1. Sadaghiani S, Hesselmann G, Kleinschmidt A. Distributed and antagonistic contributions of ongo-ing activity fluctuations to auditory stimulus detection. *J of Neuroscience*, 29(42): 13410-7.
    - I (SS) designed the experiment, acquired the data, analyzed the data and wrote the paper.
    - GH gave advice in data analysis.
    - AK designed the experiment and wrote the paper as supervising author.
2. Sadaghiani S, Scheeringa R, Lehongre K, Morillon B, Giraud AL, Kleinschmidt A (2010) Intrinsic Connectivity Networks, Alpha Oscillations and Tonic Alertness: A simultaneous EEG/fMRI Study. *J of Neuroscience*, 30(30):10243-50.
    - I (SS) designed the experiment, analyzed the data and wrote the paper.
    - RS: analyzed part of the data. KL, BM and ALG acquired the data.
    - AK designed the experiment and wrote the paper as supervising author.
3. Sadaghiani S*, Hesselmann G*, Friston KJ, Kleinschmidt A (2010) Predictive coding or evidence accumulation? False inference and neuronal fluctuations. *PLoS One* 5(3): e9926. doi:10.1371/journal.pone.0009926. *shared first-authorship.
    - I (SS) and GH, with equal contribution, designed the experiment, acquired the data, analyzed the data and wrote the paper.
    - KJF contributed to writing the paper.
    - AK designed the experiment and wrote the paper as supervising author.
4. Sadaghiani S, Hesselmann G, Friston KJ, Kleinschmidt A (2010) The relation of ongoing brain activity, evoked neural responses, and cognition. *Frontiers in Systems Neuroscience* 4(20): doi:10.3389/fnsys.2010.00020.
    - I (SS) wrote the paper.
    - GH and KJF contributed to writing the paper.
    - AK wrote the paper as supervising author.

2.2 Sadaghiani et al. (2009)
Distributed and Antagonistic Contributions of Ongoing Activity Fluctuations to Auditory Stimulus Detection.

Behavioral/Systems/Cognitive

Distributed and Antagonistic Contributions of Ongoing Activity Fluctuations to Auditory Stimulus Detection

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Recent studies have shown that ongoing activity fluctuations influence trial-by-trial perception of identical stimuli. Some brain systems seem to bias toward better perceptual performance and others toward worse. We tested whether these observations generalize to another as of yet unassessed sensory modality, audition, and a nonspatial but memory-dependent paradigm. In a sparse event-related functional magnetic resonance imaging design, we investigated detection of auditory near-threshold stimuli as a function of prestimulus baseline activity in early auditory cortex as well as several distributed networks that were defined on the basis of resting state functional connectivity. In accord with previous studies, hits were associated with higher prestimulus activity in related early sensory cortex as well as in a system comprising anterior insula, anterior cingulate, and thalamus, which other studies have related to processing salience and maintaining task set. In contrast to previous studies, however, higher prestimulus activity in the so-called dorsal attention system of frontal and parietal cortex biased toward misses, whereas higher activity in the so-called default mode network that includes posterior cingulate and precuneus biased toward hits. These results contradict a simple dichotomic view on the function of these two latter brain systems where higher ongoing activity in the dorsal attention network would facilitate perceptual performance, and higher activity in the default mode network would deteriorate perceptual performance. Instead, we show that the way in which ongoing activity fluctuations impact on perception depends on the specific sensory (i.e., nonspatial) and cognitive (i.e., mnemonic) context that is relevant.

Introduction

Despite its ubiquitous prevalence, spontaneous activity has conceptually long been considered technical or biological "noise" and has been discarded as unexplained variance when estimating average evoked neural responses to an externally imposed paradigm. Yet, ongoing activity fluctuations contribute to variability of evoked responses (Arieli et al., 1996) and impact on perceptual performance (Linkenkaer-Hansen et al., 2001; Boly et al., 2007; Hesselmann et al., 2008a,b). These effects range from focal observations in functionally specialized regions to distributed patterns involving areas that are less specifically related to task demands.

Perceptual performance is affected by variations of preceding ongoing (Boly et al., 2007) or evoked (Li et al., 2007; Eichele et al., 2008) activity in neuroanatomical systems that resemble those networks which functional neuroimaging studies have defined on the basis of coherent spontaneous fluctuations during resting wakefulness (Fox and Raichle, 2007). One of these so-called resting-state networks that comprises posterior cingulate and precuneus, the temporoparietal junction, and medial prefrontal regions will stereotypically deactivate during a typical sensorimotor or cognitive task. This task-negative behavior correlates with the degree of functional challenge (McKiernan et al., 2003; Greicius and Menon, 2004; Mason et al., 2007; Singh and Fawcett, 2008) and has been taken as a possible sign of suspending a default mode of brain function (Gusnard and Raichle, 2001). Another network of bilateral frontal and parietal regions is involved in attentional control, and of all resting-state networks, its activity is least correlated with that in the default-mode network (Fox et al., 2005; Fransson, 2005). Together with other systems, this network usually shows task-positive behavior, i.e., activation when subjects are engaged in a paradigm.

These observations could indicate that higher ongoing activity in sensory and attentional brain systems facilitates perceptual performance, whereas higher activity in regions of the default mode network deteriorates perceptual performance. The present study sought to explore several related issues. Our starting hypothesis was that where and how ongoing activity impacts on perceptual performance is strongly context dependent. Our own previous studies with perceptual decisions on supraliminal but ambiguous visual stimuli identified effects from ongoing activity only in those brain regions where functional specialization matched the perceptual feature to be judged (Hesselmann et al., 2008a,b). We hypothesized that for detection of near-threshold stimuli, effects would be unveiled not only in specifically related sensory cortex but also in other more generic brain systems as suggested by a somatosensory study (Boly et al., 2007). We also sought to test whether previous observations in the visual

Received May 29, 2009; revised Sept. 2, 2009; accepted Sept. 21, 2009.

This work was funded by the Agence Nationale de la Recherche (SPONTACT; France). S.S. is supported by the Friedrich-Ebert Foundation (Germany). This fMRI experiment was part of a general research program on functional neuroimaging of the human brain, which was sponsored by the Atomic Energy Commission (Denis Le Bihan). We thank Evelyn Eger for helpful comments on data analysis.

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DOI:10.1523/JNEUROSCI.2592-09.2009

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(Hesselmann et al., 2008a,b) and sensorimotor system (Boly et al., 2007; Fox et al., 2007) generalize to the auditory modality where evidence is so far lacking. We hence chose an auditory task that relies more on recognition and less on spatial orienting than somatosensory and visual perception and focused on the relation of stimulus detection and prestimulus activity in auditory cortex as well as the aforementioned task-positive and task-negative systems.

Materials and Methods

Subjects, imaging data acquisition, and paradigm. Twelve right-handed normal-hearing subjects (two female; ages, 19–30) gave written informed consent before participation in imaging on a 3T magnetic resonance imaging (MRI) whole-body scanner (Tim-Trio; Siemens). The study received ethics committee approval by the authorities responsible for our institution. One subject reported to have fallen asleep in one session and was thus excluded from analysis. Anatomical imaging used a T1-weighted magnetization-prepared rapid acquisition gradient echo sequence [176 slices, repetition time (TR) = 2300 ms, echo time (TE) = 4.18 ms, filed of view (FOV) 256, voxel size $1 \times 1 \times 1$ mm). Functional imaging used a T2*-weighted gradient-echo, echo-planar-imaging sequence (25 slices, TR = 1500 ms, TE = 30 ms, FOV 192, voxel size $3 \times 3 \times 3$ mm). Stimulus presentation and response recording used the Cogent Toolbox (John Romaya, Vision Lab, UCL; www.vislab.ucl.ac.uk) for MATLAB (Mathworks) and sound delivery a commercially available MR-compatible system (MR Confon).

We acquired in the same subjects at an earlier occasion 820 volumes of task-free "resting state" data (with closed, blind-folded eyes) and then, on a later occasion, experimental sessions of 820 volumes each during which subjects were exposed to sparse near-threshold auditory stimuli and performed an auditory detection task. An additional passive localizer run for defining auditorily responsive brain regions was acquired after the main experiment. This 81 volume run consisted of three 20 s blocks of repetitive stimulus presentation with 0.5 s interstimulus intervals (ISI) at clearly audible volume separated by 15 s baseline epochs.

The auditory stimulus was a 500 ms noise burst with its frequency band modulated at 2 Hz (from white noise to a narrower band of 0–5 kHz and back to white noise). Subjects were blindfolded and instructed to report as quickly and accurately as possible by a right-hand key press whenever they heard the target sound despite scanner's background noise. In a first 6.5 min run, which was not analyzed, we determined each subject's auditory threshold using a simple staircase procedure. We refer to auditory threshold as the signal level for which the probability of detection is 50%. The staircase procedure started out at a clearly audible volume and applied a simple up–down rule (von Békésy, 1960) with 25 trials and interstimulus intervals randomized between 2.5 and 5 s. The signal level of the last 6 trials was averaged to yield an estimate of subjects' threshold. Next, each subject performed two and some subjects three experimental runs of 20 min duration. On each run, target stimuli were presented at individual threshold (periliminal stimuli) on 36 trials and at a fixed suprathreshold level on 4 "catch" trials. ISIs ranged unpredictably from 20 to 40 s, with each specific ISI used only once. Before each run, the target stimulus was played a few times at suprathreshold volume for (re)memorization, and subjects were informed that in most of the trials the target sound would be played at a barely perceptible level. If within 1.5 s of stimulus onset a key was pressed, this trial was counted as a hit, if not as a miss. All other key presses were classified as false alarms.

Standard analysis of functional magnetic resonance imaging data. We used statistical parametric mapping (SPM5, Wellcome Department of Imaging Neuroscience, UK; www.fil.ion.ucl.ac.uk) for image preprocessing (realignment, coregistration, normalization to MNI stereotactic space, spatial smoothing with a 5 and 6 mm full-width at half-maximum isotropic Gaussian kernel for single-subject and group analyses, respectively) and estimation of general linear models with a high-pass filter of 1/128 Hz and realignment parameters as nuisance covariates.

Regressors for event-related analysis were obtained by convolving for each condition unit impulse time series with a canonical hemodynamic response function. The statistical model included the four events hits, misses, false alarms, and catch trials. Timing of false alarm events (response in the absence of an external stimulus) was defined based on the subject's mean reaction time in hits. For each subject, we estimated condition-specific effects using a general linear model, then created contrast images and entered these into a second-level one-sample *t* test.

Unless otherwise stated, we report activations of this standard analysis at $p < 0.05$ corrected at the cluster level for multiple comparisons using an auxiliary (uncorrected) voxel threshold of $p < 0.0001$. This auxiliary threshold defines the spatial extent of activated clusters, which form the basis of our (corrected) inference. Results are rendered onto an inflated average brain as provided by FreeSurfer (CorTechs Labs; http://surfer.nmr.mgh.harvard.edu) with the help of SPM SurfRend toolbox (http://spmsurfrend.sourceforge.net).

Resting state functional connectivity analysis. We used a 20 min task-free session recorded in each of the subjects on an earlier occasion to analyze resting-state functional connectivity (rs-fc). We thereby defined the default mode network as well as two other large-scale networks, one related to spatial attention and another to "task set maintenance" (Dosenbach et al., 2006, 2007). In the context of our study, we preferred to label the latter system as an "intrinsic alertness" network for the following reasons: This label allowed us to pay tribute to results involving this network in previous functional neuroimaging studies probing auditory intrinsic alertness (Sturm et al., 2004) and to the role that alertness has been assigned in performance fluctuations during long-lasting auditory detection tasks (Makeig and Inlow, 1993). Seed regions for calculation of rs-fc networks were the gray-matter voxels in a sphere of 10 mm radius centered on stereotactic coordinates reported in three meta-analyses by other laboratories: (1) Posterior cingulate cortex (PCC)/precuneus (−5, −49, 40) and medial prefrontal cortex (MPFC)/ventral anterior cingulated cortex (vACC) (−1, −47, 4) for the default mode network (Fox et al., 2005); (2) right intraparietal sulcus (IPS) (27, −58, 49) and right frontal eye fields (FEF) (24, −13, 51) for the dorsal spatial attention system (Fox et al., 2006); and (3) right anterior insula (36, 16, 4) and right anterior thalamus (10, −15, 8) for the intrinsic alertness system. While coordinates for the latter system were hence derived from studies revolving around task set maintenance (Dosenbach et al., 2007), it should be pointed out that those as well as our results partially overlapped with results from studies that used slightly different seed regions in the anterior insula and that provided other functional interpretations for their findings (Seeley et al., 2007; Eckert et al., 2009). We, therefore, preferred to apply a label to this network that was intuitively plausible within the context of our own present study.

For each of six seed regions, the high-pass (1/128 Hz)-filtered signal time course was averaged across all respective voxels and used as a regressor of interest in a separate general linear model. Imaging data were preprocessed as described above. In addition to the same nuisance variables as in the activation experiment, we also included the global signal of three separate brain compartments (all white matter voxels, all gray matter voxels, and all CSF voxels) as covariates of no interest. Contrast images corresponding to each regressor were created for each subject and entered into a second-level one-sample *t* test for each seed region. Again, maps were rendered onto a canonical average brain provided in FreeSurfer.

Definition of regions of interest. We defined several regions of interest (ROIs) from which we extracted time course data estimated in a finite impulse model procedure. Voxels responding to the auditory stimulus were defined on a subject-by subject basis in two steps. First, at the group level, the contrast periliminal stimuli (i.e., hits and misses) > baseline ($p < 0.001$) was masked by the passive auditory localizer contrast at $p < 0.001$. A spherical search space of 10 mm was defined around the peak of the periHeschl clusters with the highest *z* score [right hemisphere: (42, −6, −12), $z = 4.14$, 94 voxels and left hemisphere: (−42, −18, −6), $z = 3.9$, 23 voxels]. Next, for each subject's corresponding first-level contrast, all voxels within this search space were selected that passed a lenient threshold ($p < 0.05$, uncorrected).

Further ROIs were defined from the rs-fc maps (see above). For every subject, default mode, spatial attention, and intrinsic alertness networks were defined as those voxels whose time course significantly correlated at $p < 0.001$ (uncorrected) with that of both respective seed regions. The resulting subject-specific rs-fc networks were then further constrained by masking with the corresponding group result. These group masks were defined at a second level of analysis as the overlap of corresponding pairs of rs-fc networks from either seed region at threshold $p < 0.005$, uncorrected, and cluster extent >200 voxels. The right and left middle temporal complex (MT+) clusters (31 and 14 voxels in the conjunction analysis) were also included in the group mask of the spatial attention system, because they have been considered one of the system's core constituents in cognitive studies (Corbetta and Shulman, 2002) and in rs-fc studies (Fox et al., 2006). In the group statistical map of the intrinsic alertness system, bilateral anterior insula and anterior thalamus merged into a single big cluster. To enable separate investigation of these regions, the map was masked by anatomically defined masks of insula and thalamus, respectively (WFU PickAtlas 2.4, Wake Forest University School of Medicine; http://www.fmri.wfubmc.edu/cms/software).

For each subject, the resulting networks as a whole and each of their clusters in isolation were used as ROI for time course extraction.

Statistical analysis of functional magnetic resonance imaging signal time courses. After the aforementioned spatial preprocessing, we used a temporal high-pass filter with very low cutoff (1/1000 Hz) and no prewhitening. This ensured linear drift removal, a common practice in many related studies to deal with technical noise sources (Golland et al., 2007; Hesselmann et al., 2008a,b), while minimizing interference with low frequency brain activity fluctuations. A finite impulse response (FIR) model was applied using 24 peristimulus stick functions (×1.5 s bins) for each of the four conditions, hits, misses, false alarms, and catch trials. Nuisance covariates included the realignment parameters.

The estimated time course was then averaged across voxels of specific ROIs. Condition-dependent time courses were indistinguishable for corresponding regions of the two hemispheres and therefore collapsed. For each ROI, a paired t test of "perceptual outcome" was performed for the hemodynamic signal at the immediate prestimulus time point 0 s. This time point was chosen because it is the latest epoch that is with certainty not yet contaminated by stimulus-evoked activity. Accordingly, it has proven informative to predict perceptual outcome in earlier related studies (Hesselmann et al., 2008a,b). Based on our previous observations, we tested one-tailed in the auditory ROI, where we hypothesized prestimulus signal to be larger for detected stimuli and two-tailed in all other ROIs. For display purposes, but not statistical analyses, signal time courses were temporally smoothed with a (1, 2, 1) kernel.

The FIR model was also used to generate a map of prestimulus effects on auditory detection by contrasting parameter estimates for hit and miss trials at time point 0 s. The corresponding contrast images were entered into a second-level one-sample t test. We report results of this analysis at $p < 0.05$ cluster-level significance after applying an auxiliary voxel-level threshold of $p < 0.01$ and extent threshold >50 voxels.

Results

A group of 11 subjects performed a detection task on auditory stimuli presented at their individually determined detection threshold in a very sparse event-related functional MRI (fMRI) paradigm with highly variable ISI ranging from 20 to 40 s.

Behavioral findings

Overall, the stimulus was detected in slightly more than half of periliminal trials (62.2 ± 17% hits). The individual hit–miss ratio was largely consistent across separate sessions, with the exception of one session each in two of the subjects with 94.4% hits (i.e., only two misses). Subjects' accuracy in detecting the rare supraliminal catch stimuli was 93.2 ± 0.1%. Reaction times were 788 ± 102 ms for detected periliminal stimuli (hits) and 578 ± 142 ms for detected catch trials. Subjects reported a highly variable number of false alarms. Many sessions had no false alarms at all, although each subject reported at least one false alarm. The median of false alarms per session (within-subject average across sessions) was median = 4.5 ± interquartile range = 6.9.

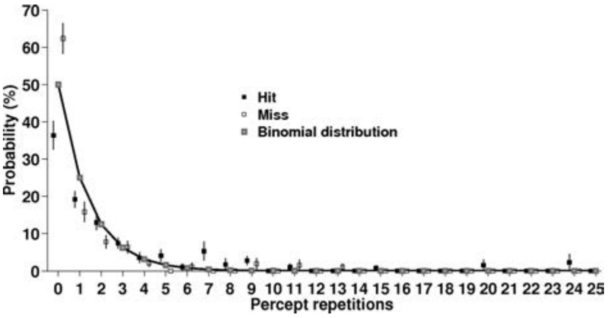

Figure 1. Distribution of percept repetitions. The incidence of repetitions for hits and misses is well approximated by a binomial distribution (goodness-of-fit $R^2 = 0.93$ for hits, $R^2 = 0.83$ for misses).

The incidence of percept repetitions was well approximated by a binomial distribution indicating approximately stochastic stimulus detection and hence independence of successive trials (Fig. 1). The probability for different perceptual outcomes in two immediately successive trials (i.e., "zero repetition") reflected the slight overall bias for hits. Finally, there was no bias for misses to occur after shorter or longer ISIs than hits. The length of prestimulus ISIs was indistinguishable (paired t test $p = 0.6$) between hits (30.6 ± 0.7 s) and misses (30.3 ± 1 s).

Imaging results

Figure 2 shows statistical parametric maps of evoked responses. Hits versus baseline involved distributed activation in a large set of cortical and subcortical areas summarized in supplemental Table 1, available at www.jneurosci.org as supplemental material. Misses versus baseline did not yield significant activation in these maps ($p < 0.001$, uncorrected), nor did misses versus hits. A direct comparison of hits versus misses revealed an activation pattern very similar to hits versus baseline with an additional activation in the cerebellum (supplemental Table 1, available at www.jneurosci.org as supplemental material).

Signal time course of early auditory cortex

Figure 3 shows the time course from the bilateral auditory region. Voxels in auditory cortex responding to the periliminal stimulation (hit and miss > baseline) were selected for time course extraction on a subject-by-subject basis. They were restricted to a search sphere that was defined at group level by masking activation foci of periliminal stimulation with a mask obtained from a passive auditory localizer session. The Talairach coordinates [42, −6, −12 and −42, −18, −6] of the search sphere are in good agreement with cytoarchitectonic (Morosan et al., 2001) and functional (Scott and Johnsrude, 2003) descriptions of Heschl's gyrus and presumably include parts of primary auditory cortex. Based on previous results (Hesselmann et al., 2008a,b), we tested the immediate prestimulus time point 0 s for percept-dependent differences in BOLD signal time course. As hypothesized, we found slightly but significantly higher prestimulus baseline signal in hits than in misses ($t_{(1,10)} = 2.21$, $p = 0.025$ one-tailed).

Signal time course of functional networks

We next investigated the signal time course in a set of distributed networks and their constituent regions. The spatial patterns of rs-fc networks that we obtained here are in good agreement with previous studies (Greicius et al., 2003; Fox et al., 2005; Fransson, 2005; Dosenbach et al., 2007; Seeley et al., 2007). Figure 4 shows each network as defined from an independent resting-state ses-

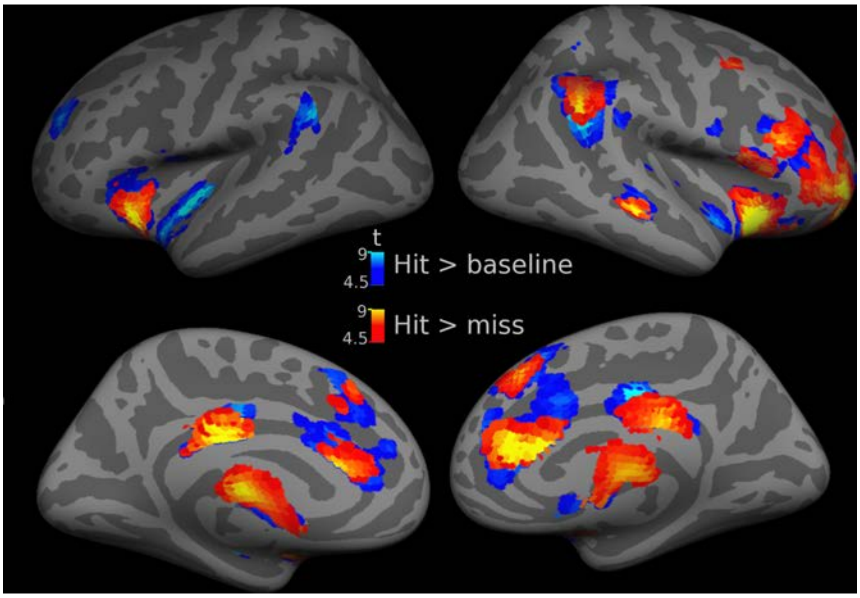

Figure 2. Spatial distribution of evoked cortical responses during successful stimulus detection. Activations evoked in hit trials versus baseline are shown in cold colors (for details, compare supplemental Table 1, available at www.jneurosci.org as supplemental material). A direct comparison of greater responses during hits than misses (warm colors) revealed a very similar activation pattern. Threshold height $p < 0.05$ corrected at the cluster level using an auxiliary (uncorrected) voxel threshold of $p < 0.0001$. Group results ($n = 11$) are superimposed onto the lateral and medial aspects of an inflated cortical surface of a canonical average brain.

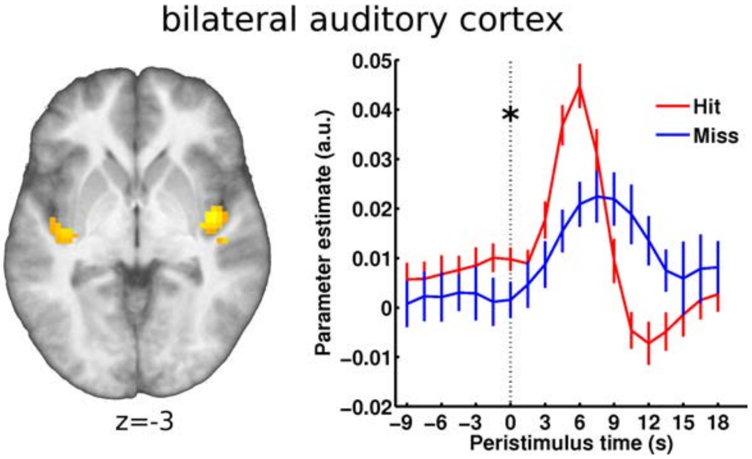

Figure 3. Prestimulus fMRI time courses from bilateral auditory cortex. Left, Map of activation evoked by the near-threshold stimulus (independent of percept) assessed in a group analysis. This map served as the basis for subject-by-subject definition of the auditory ROI (shown on the group's average brain; threshold height $p < 0.001$ uncorrected; see Materials and Methods for details). Right, In accord with our previous findings, we tested the effect of prestimulus activity at time point 0 s and found significantly higher activity preceding hits than misses (as indicated by an asterisk). Error bars indicate ±SEM.

sion by rs-fc analysis. It also shows the corresponding signal time courses in the auditory detection sessions. For each system as a whole and for each of its constituent regions in isolation, these signal time courses were tested for differences at time point 0 s as a function of perceptual outcome.

The dorsal attention system showed higher prestimulus activity preceding misses than hits ($t_{(1,10)} = 3.82, p < 0.005$). On a region-by-region level, this effect was significant in IPS ($t_{(1,10)} = 4.21, p < 0.005$) and MT+ ($t_{(1,10)} = 2.23, p < 0.05$) but not in FEF. Interestingly, task-positive behavior was preserved in the evoked responses during hit trials, whereas misses showed a blunted pattern, if any stimulus-locked response at all. In contrast, hits were preceded by significantly higher prestimulus baseline activity in the default mode network than misses (whole system: $t_{(1,10)} = 2.43, p = 0.036$). This effect was driven by the PCC/precuneus component ($t_{(1,10)} = 2.61, p = 0.026$), whereas the baseline signal difference did not reach significance in MPFC/vACC or lateral parietal cortex. Again, task-negative behavior was conserved across all regions but only in hit trials, and it appeared fairly late in relation to stimulus timing. Moreover, in the precuneus, the heightened prestimulus signal in hit trials evolved into an early but stimulus-locked task-positive response that was absent in miss trials.

Activity fluctuations in these two aforementioned networks, the dorsal attention system and the default mode network, have been described to be intrinsically anticorrelated or rather to show the lowest degree of correlation of all resting-state networks (Fox et al., 2005, 2009; Fransson, 2005). Inverse correlations with performance across the two systems could then be ascribed to a source in merely one system and an epiphenomenon in the other. Visual inspection of the time courses renders this interpretation unlikely for our experiment. The prestimulus signal in the dorsal attention system that is associated with misses shows a slow build-up over time and that in the default mode network associated with hits shows a very brief build-up before stimulation, in each instance without mirroring signal behavior in the respective other system. And the evoked responses showed task-positive behavior in both the dorsal attention system and the precuneus, which also renders a hard-wired antagonistic relation unlikely.

Finally, in the intrinsic alertness system, hits were preceded by greater prestimulus activity than misses ($t_{(1,10)} = 3.86, p < 0.005$). This pattern was consistent across all regions of this network (anterior thalamus: $t_{(1,10)} = 3.76, p < 0.005$; dorsal ACC: $t_{(1,10)} = 3.6, p < 0.005$ and trend in anterior insula: $t_{(1,10)} = 2.23, p = 0.05$). While the intrinsic alertness system is also in general found to be as much anticorrelated with the default mode network as the dorsal attention system (Fox et al., 2005; Fransson, 2005), its behavior was nonetheless opposite to the one in the dorsal attention system.

As in our previous studies, we performed a voxel-by-voxel mapping of the prestimulus effect by computing the contrast of the estimated signal at time point 0 s as a function of perceptual outcome (Fig. 5). This allowed investigating whether the effects observed in a priori defined ROIs were spatially specific to those regions. At the whole-brain mapping level, the prestimulus effect at time point 0 s on stimulus detection was significant ($p < 0.05$

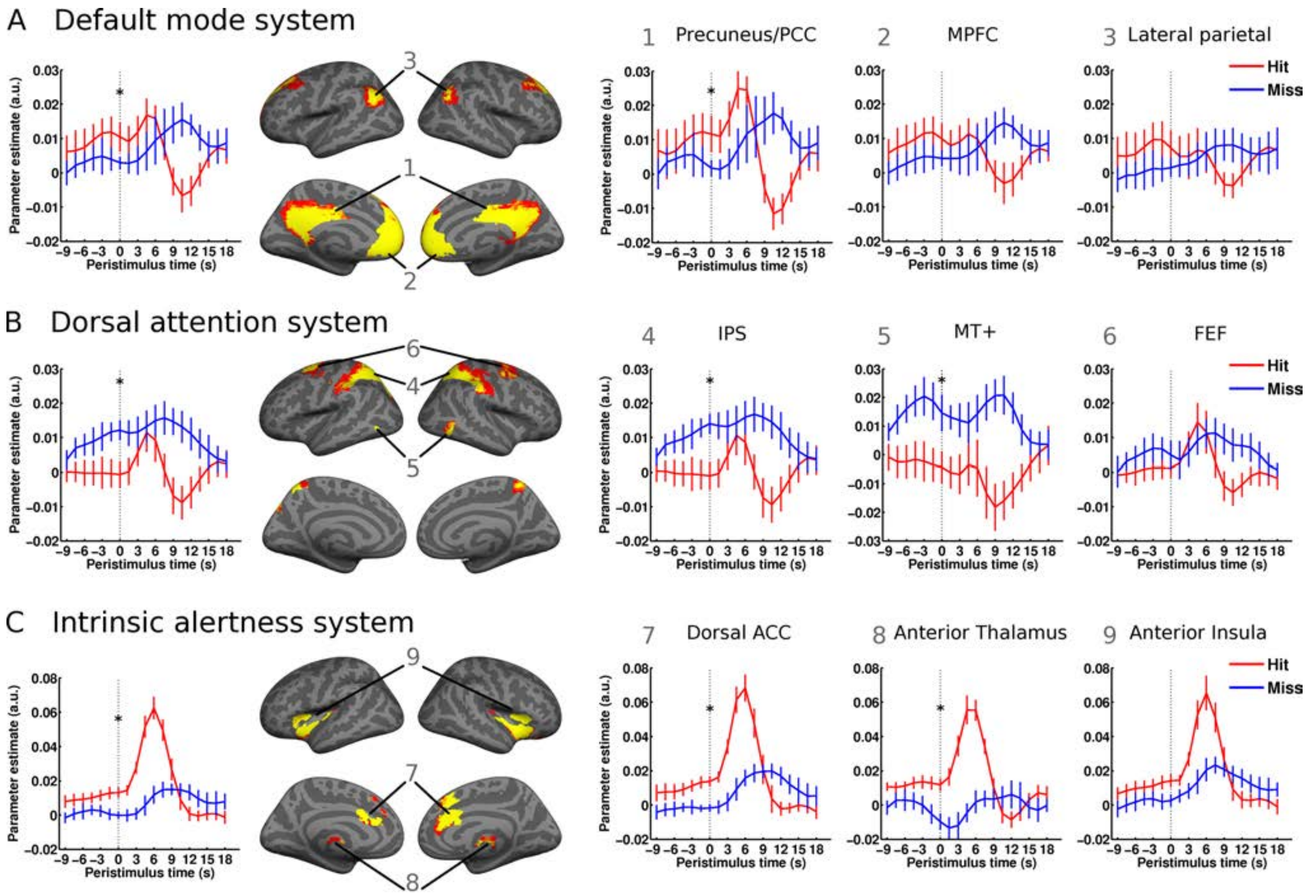

Figure 4. Prestimulus time courses from resting-state functional connectivity (rs-fc) networks. Left, Time courses averaged over the complete rs-fc systems. Middle, Rs-fc networks as defined by seed-based analysis of a resting-state scanning session. Numbers indicate regions of interest for which peristimulus activity time courses are plotted in the right-hand panels. Right, Time courses of individual regions of the respective network. While higher signal levels in the default mode system (***A***) and the intrinsic alertness system (***C***) were found before successful stimulus detection, higher signal in the dorsal attention system (***B***) preceded misses. Asterisks indicate significant percept-dependent time course difference at time point 0 s. Error bars indicate ±SEM.

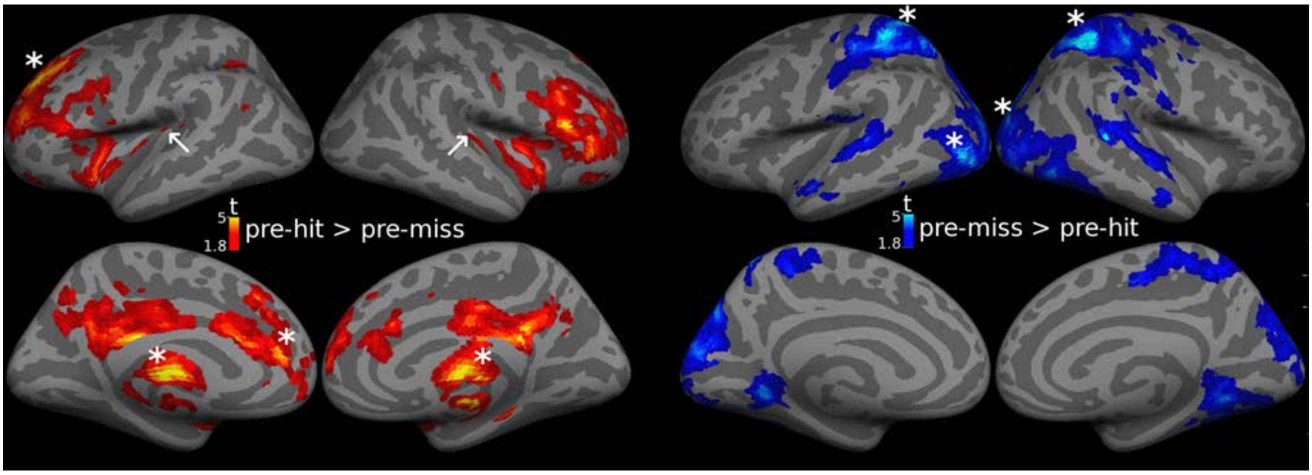

Figure 5. Statistical parametric maps of difference in prestimulus activity between hit and miss trials. Signal at time point 0 s (as estimated in the FIR-model, see Materials and Methods) was contrasted between hit and miss trials. The resulting second-level maps are shown at $p < 0.05$ uncorrected to illustrate spatial specificity of prestimulus activity biasing for hits (left) and misses (right), respectively. Asterisks indicate regions with significant effects after correction for multiple comparisons. White arrows indicate Heschl's gyri. Signal time courses over the full peristimulus window are shown in Figures 3 and 4 for largely corresponding but independently defined ROIs and rs-fc networks.

at cluster level after voxel-level threshold of $p < 0.01$ and extent threshold >50 voxels) in the following regions: dorsal ACC [146 voxels, (−15, 39, 3), $z = 3.71$, $p = 0.034$], an extended cluster [1064 voxels, (27, 0, 12), $z = 4.35$, $p < 0.001$] containing thalamus [left: (−12, −21, 12), $z = 4.27$; right: (21, −15, 15), $z = 4.04$] and left superior frontal gyrus [143 voxels, −18, 39, 36), $z = 3.74$, $p = 0.038$] showed significantly higher prestimulus signal for hits than misses. Conversely, IPS [right: 477 voxels, (30, −48, 57), $z =$

3.88, $p < 0.001$; left: 347 voxels, (−27, −45, 54), $z = 3.82$, $p < 0.001$] and posterior occipital cortex [left: 386 voxels, (−27, −93, −18), $z = 3.49$, $p < 0.001$; right: 367 voxels, (15, −90, 21), $z = 3.34$, $p < 0.001$] showed higher prestimulus signal for misses than hits. The latter significant effects in the visual system extended beyond MT+ to further regions of the dorsal visual system similar to descriptions of the dorsal attention system based on rs-fc (Fox et al., 2006).

Discussion

One popular and informative approach in studying the neural correlates of consciousness has been to compare evoked neural responses to perceived and nonperceived stimuli. As neural responses in themselves are sensitive to changes in stimulus properties, it is important that the correlation with conscious perception be assessed for identical stimuli. Several studies have evoked human brain responses and determined when and where stimulus-locked signal time courses show significant signal differences as a function of perceptual outcome (Ress et al., 2000; Pessoa and Padmala, 2005; Sergent et al., 2005; Pourtois et al., 2006). Instead of following the stimulus-evoked neural activity trace, however, one can ask what in turn may provide a neural source for this variability in neural responses to identical stimuli. Previous work has linked response variability to fluctuations in ongoing activity immediately before stimulation (Arieli et al., 1996).

Functional significance of prestimulus activity variations has been found in cued perceptual paradigms in nonhuman and human primates. In animal studies, effects on evoked responses (Arieli et al., 1996) and perceptual performance (Supèr et al., 2003) have been confined to a very short prestimulus time window, but the fMRI work in humans that relies on hemodynamic signals has uncovered effects with slower time constants (Sapir et al., 2005). While prestimulus effects in cued paradigms can be thought of as the variability in response to a cue the functional importance of slow spontaneous variations of ongoing activity has been shown in other studies. A prominent feature in ongoing electrical brain activity is the prevalence of oscillations that occur in various frequency bands. Over time, these different frequency bands display flexible adjustments in their phase synchrony as well as slow modulations in their overall power (Palva et al., 2005; Schroeder and Lakatos, 2009). Recordings of such modulations of large-scale oscillatory signals have been found to affect perceptual performance (Linkenkaer-Hansen et al., 2001; Monto et al., 2008). The precise relationship between the brain oscillations as well as slow cortical potentials and hemodynamic signals used in fMRI is not yet fully understood (He and Raichle, 2009), but the existing data suggest that the dynamics of ongoing activity are critical for the fate of incoming sensory information and include low frequency components (Buzsáki, 2006).

Following this line of thought, we have recently shown a biasing effect of fairly slow prestimulus activity variations onto subsequent perception of faces from an ambiguous figure (Hesselmann et al., 2008b) and of coherent motion in a moving dot kinematogram at threshold coherence (Hesselmann et al., 2008a). These effects were specific to the relevant sensory regions, namely the fusiform face area and the visual motion complex (hMT+), respectively. Here, we report a generalization of this finding beyond the visual domain to audition. In the auditory area responsive to our near-threshold stimulus, we found that higher prestimulus activity biased toward detecting the stimulus, whereas low activity levels more likely yielded misses. This observation confirms our previous findings that ongoing activity levels in sensory areas impact on how several seconds later specifically related input will be perceived. As in our previous studies, this effect was rather weak potentially reflecting a truly small neuronal effect or alternatively sensitivity limitations of the neuroimaging technique. However, and different from our previous findings, the present study disclosed much stronger effects from ongoing activity in distributed functional networks that we had defined in an independent resting-state session.

We had anticipated such a difference because our present study involved detection of near-threshold stimuli in a free-response setting instead of two alternative forced choice decisions on ambiguous but clearly notable stimulation as in our earlier work. In accord with this view, evoked responses differed between hits and misses not only in auditory cortex but also in many other brain regions, likely reflecting all those processes that come into play once a stimulus will drive a behavioral response. Detailed discussion of these rather trivial effects is beyond the scope of our interest. One aspect of evoked responses, however, is relevant for our question. Peristimulus time courses of hit trials showed task-positive behavior in all three resting-state networks that we studied, including parts of the default mode network where the majority of paradigms elicit deactivation (Shulman et al., 1997; Binder et al., 1999; McKiernan et al., 2003). The latter network also showed the strongest inter-regional variation in that only the precuneus displayed a clear task-positive response that was followed by the same delayed deactivation as in the other constituent regions. Such a biphasic response pattern has previously been demonstrated in the precuneus in a memory-dependent “transverse-patterning task” and related to associative memory processes (Meltzer et al., 2008).

The key issue of our study was to detect if and how baseline fluctuations in these resting-state networks bias detection of near-threshold auditory stimuli. Extending the observation of task-positive behavior in the precuneus, we found significantly higher activity in hit trials already before the evoked response. This observation may appear surprising, because previous work has associated activity levels in the precuneus with introspective, retrospective, or prospective mental processes (Buckner and Carroll, 2007; Mason et al., 2007; Botzung et al., 2008) and accordingly with deteriorated perceptual performance (Weissman et al., 2006; Boly et al., 2007; Eichele et al., 2008). It is important to note that those latter observations were made in paradigms in the somatosensory and visual modality that inevitably imposed a strong load on spatially selective attention. Conversely, in our study, discriminating a meaning-free broadband diotic stimulus from the continuous and qualitatively similar background (scanner) noise cannot be linked to fluctuations in spatial attention but rather to variations in the degree to which the mnemonic trace of this previously presented target stimulus was available to the subjects. As activity in the precuneus and adjacent retrosplenial and posterior cingulate cortex has been linked to retrieval success (Shannon and Buckner, 2004), we interpret our findings in the precuneus to indicate a facilitating effect of mnemonic mechanisms on recognition of the target stimulus. This interpretation is grounded in a view on ongoing activity as a carrier of dynamic predictions about future events (Fox and Raichle, 2007) and in line with our previous observations (Hesselmann et al., 2008a,b). A more general conclusion is that—as in other studies—the nature of ongoing activity is likely to reflect contextual effects, even a sparse paradigm being one of several relevant factors.

Further support for this interpretation comes from the findings we obtained in the dorsal spatial attention network and associated areas of the dorsal visual stream [even though the latter could also reflect intrinsic mechanisms of low-level cross-modal competition, see Laurienti et al. (2002)]. While generally associated with improved perceptual performance in paradigms requiring selective spatial attention (Burton and Sinclair, 2000; Corbetta and Shulman, 2002), activity in the dorsal attention system proved detrimental to stimulus detection in our paradigm, again presumably expressing the lack of spatial connotation in our stimulus and task. Our findings suggest that higher ongoing activity in the dorsal attention network favors the processing of spatial information and that this might compete with nonspatial attention for similar central resources. Interestingly, however, the dorsal attention system did show clear-cut task-positive behavior in hit trials, i.e., evoked responses when stimuli were detected, which may reflect an automatic recruitment of spatial mechanisms by behaviorally relevant stimuli.

In the third resting-state network that we assessed and that we refer to as intrinsic alertness system, higher prestimulus activity level facilitated subsequent stimulus detection. Functionally, this effect in a paradigm which instructed subjects to continuously monitor auditory input for potential target occurrence, is readily related to mechanisms proposed in previous studies emphasizing task set maintenance (Dosenbach et al., 2007) or "salience" (or arousal) (Seeley et al., 2007). And similar to the network in those studies the one defined here also includes the anterior cingulate, anterior insula, and thalamic components. Together with the dorsal attention system and more ventral frontal and parietal regions, this network has been associated with "task-positive" behavior (Fox et al., 2005; Fransson, 2006). In our study, however, the effect of prestimulus signal in the intrinsic alertness network on stimulus detection was opposite in sign to that in the dorsal attention system and identical in sign to that from the default mode system. It hence appears likely that instead of a hard-wired generic relationship between these three networks, genuine and distinct effects of activity in all of them contributed independently to perceptual performance.

Conclusion

Together, our data contribute to a growing body of evidence that converges across species and signal modalities in linking variability of neural responses and behavioral performance to low frequency dynamics of ongoing brain activity. Our experiment illustrates that site and sign of these interactions depend on functional context. Beyond an expected local effect in accordingly specialized sensory cortex, we found performance in a free-response detection setting to be differentially affected by prestimulus activity levels in distributed functional networks. In contrast to previous related studies, higher prestimulus signal not only in the cingulo-insular intrinsic alertness system but also in the default mode network facilitated stimulus detection, whereas higher activity in the dorsal attention system was detrimental to perceptual performance. We hence conclude that the actual effects of ongoing activity fluctuations on processing subsequent stimuli do not only depend on the brain network where they occur but also on the functional context that is defined by the paradigm one uses to probe these effects. These findings speak against a simple dichotomic account of activity in these distributed networks and underline the flexibility with which their cooperation can change as a function of variable functional demands.

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Supplementary table 1
Evoked responses during successful stimulus detection.

	Talairach coordinates	z	voxel	p corrected
Hit > baseline				
Angular/supramarginal gyri	right 54 -48 27	5.57	464	<0.001
	left -60 -51 30	4.54	55	0.001
Superior temporal sulcus	right 51 -27 -9	4.43	55	0.001
Auditory cortex	right 42 -6 -15	4.34	29	0.009
	left -39 -18 -9	5.32	99	<0.001
Striatum	right 18 15 -9	4.86	1963	<0.001
	left -18 6 9	4.11		
Insula	right 30 15 -9	4.54		
	left -27 15 -9	4.46		
Thalamus	right 6 -9 -6	4.09		
	left -9 -15 12	4.19		
Dorsolateral prefrontal cortex	right 36 39 36	4.20		
	45 45 15	4.17		
	39 24 21	4.15		
Inferior frontal cortex	right 57 15 15	4.60		
	left -48 3 3	4.19	30	0.008
Frontal pole	right 24 57 -9	4.56	101	<0.001
Middle cingulate cortex	bilateral 3 -15 39	5.00	183	<0.001
Anterior superior frontal sulc.	left -18 42 4	4.70	976	<0.001
Anterior cingulate cortex	bilateral 9 39 18	4.69		
Medial superior frontal gyrus	bilateral 0 21 54	4.67		
Hit > Miss				
Insula	right 24 21 -6	5.61	3469	<0.001
	left -24 15 -6	5.61		
Striatum	right 15 15 3	4.99		
	left -21 3 15	4.84		
Thalamus	right 15 -6 15	5.20		
	left -12 -15 12	5.12		
Anterior cingulate cortex	bilateral 6 36 15	5.16		
Middle cingulate cortex	bilateral -6 -18 27	4.92		
Medial superior frontal gyrus	bilateral 0 27 48	4.76		

Frontal pole	right 24 54 -9	4.93		
Dorsolateral prefrontal cortex	right 42 27 18	4.47		
	57 15 12	4.32		
Inferior frontal cortex	right 48 18 6	4.41		
Angular/supramarginal gyri	right 57 -48 33	4.91	192	<0.001
Superior temporal sulcus	right 48 -27 -12	4.89	36	0.004
Cerebellum	bilateral -6 -69 -18	4.42	92	<0.001
Middle frontal gyrus	right 42 12 54	4.24	31	0.007

$p<0.05$ corrected at the cluster level using an auxiliary [uncorrected] voxel threshold of $p<0.0001$

2.3 Sadaghiani et al. (2010a)
Intrinsic Connectivity Networks, Alpha Oscillations and Tonic Alertness: a simultaneous EEG/fMRI Study.

The Journal of Neuroscience, July 28, 2010 • 30(30):10243–10250 • **10243**

AQ: A Behavioral/Systems/Cognitive

Intrinsic Connectivity Networks, Alpha Oscillations, and Tonic Alertness: A Simultaneous Electroencephalography/Functional Magnetic Resonance Imaging Study

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Trial-by-trial variability in perceptual performance on identical stimuli has been related to spontaneous fluctuations in ongoing activity of intrinsic functional connectivity networks (ICNs). In a paradigm requiring sustained vigilance for instance, we previously observed that higher prestimulus activity in a cingulo-insular-thalamic network facilitated subsequent perception. Here, we test our proposed interpretation that this network underpins maintenance of tonic alertness. We used simultaneous acquisition of functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) in the absence of any paradigm to test an ensuing hypothesis, namely that spontaneous fluctuations in this ICN′s activity (as measured by fMRI) should show a positive correlation with the electrical signatures of tonic alertness (as recorded by concurrent EEG). We found in human subjects (19 male, 7 female) that activity in a network comprising dorsal anterior cingulate cortex, anterior insula, anterior prefrontal cortex and thalamus is positively correlated with global field power (GFP) of upper alpha band (10–12 Hz) oscillations, the most consistent electrical index of tonic alertness. Conversely, and in line with earlier findings, alpha band power was negatively correlated with activity in another ICN, the so-called dorsal attention network which is most prominently involved in selective spatial attention. We propose that the cingulo-insular-thalamic network serves maintaining tonic alertness through generalized expression of cortical alpha oscillations. Attention is mediated by activity in other systems, e.g., the dorsal attention network for space, selectively disrupts alertness-related suppression and hence manifests as local attenuation of alpha activity.

Introduction

Fn1 Recent functional neuroimaging studies have shown that evoked response variability correlates with ongoing activity fluctuations and that this variability transpires into perceptual variability (for review, see Sadaghiani et al., 2010). As a function of the paradigm, effects of ongoing activity on perceptual performance have been observed both locally in accordingly specialized areas (Hesselmann et al., 2008a,b; Sadaghiani et al., 2009) and in distributed spatial patterns that resemble resting-state or intrinsic connectivity networks (ICNs) (Boly et al., 2007; Sadaghiani et al., 2009). In some ICNs higher prestimulus activity facilitates and in others it deteriorates perceptual performance on upcoming stimuli. In a recent study using near-threshold acoustic stimuli (Sadaghiani et al., 2009), we found that prestimulus signal in frontoparietal regions including the intraparietal sulcus (IPS) and frontal eye fields biased toward missing subsequent stimuli whereas signal in auditory cortex but also in a network comprising dorsal anterior cingulate cortex (dACC), anterior insula and thalamus facilitated their detection. The former network is well characterized but the latter has remained more elusive both in terms of topography and function. Several studies have defined largely similar networks with slightly varying numbers and locations of constituent elements (Vincent et al., 2008). And others have attempted to dissect it into subnetworks linked to executive control, task-set maintenance, or salience (Dosenbach et al., 2006, 2007; Seeley et al., 2007). Yet, our paradigm with simple detection of meaning-free sparse stimuli only required maintaining tonic alertness. In accord with this interpretation, several studies that explicitly probed tonic alertness found effects in similar brain structures as we did (Sturm and Willmes, 2001; Sturm et al., 2004).

Here, we sought to further corroborate this functional interpretation. We based our investigation on results from related settings used to characterize the electroencephalographic signatures of tonic alertness in ongoing activity (Gath et al., 1983; Makeig and Inlow, 1993; Haig and Gordon, 1998). We reasoned that if our functional interpretation was correct, in the absence of any paradigm fluctuations in vigilance as indicated in the electroencephalogram should be associated with fluctuations in activity

Received Feb. 18, 2010; revised May 19, 2010; accepted June 21, 2010.

This work was funded by the Agence Nationale de le Recherche, France (ANR Grant SPONTACT). S.S. is supported by the Friedrich-Ebert Foundation (Germany). Data were acquired at the Centre de Neuroimagerie de Recherche (CENIR), Hôpital Pitié-Salpêtrière, Paris, France.

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DOI:10.1523/JNEUROSCI.1004-10.2010

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of this putative alertness network and vice versa. To test this hypothesis, we analyzed findings from simultaneous EEG and fMRI recordings during prolonged task-free resting state sessions. Previous studies have established correlations between ongoing activity in resting state networks and the expression of
AQ: C oscillatory EEG activity in different frequency bands (Laufs et al., 2003, 2006; Scheeringa et al., 2008). Remarkably, however, not even the most comprehensive attempt so far (Mantini et al., 2007) has reported findings for the network that we postulate to be involved in maintaining tonic alertness. Here, we fill this gap by showing that activity in a cingulo-insular-thalamic network is positively correlated with the GFP of oscillations in the alpha (and to some extent beta) band of the simultaneously recorded EEG. This finding matches EEG signatures of tonic alertness (Gath et al., 1983; Makeig and Inlow, 1993; Makeig and Jung, 1995; Haig and Gordon, 1998; Lockley et al., 2006; Dockree et al., 2007) and hence corroborates our previous functional interpretation of at least one functional role of this brain network.

Materials and Methods

Subjects and data acquisition. Twenty-seven healthy volunteers (ages: 19–29; 8 females; 5 left-handed; written informed consent) underwent simultaneous EEG and blood oxygen level-dependent (BOLD) fMRI. Data from one subject (female, right-handed) were excluded from analysis due to strong head motion. Subjects were requested to rest with eyes closed, stay awake, and avoid movement.

Three 10 min sessions yielded 300 echoplanar fMRI image volumes each (Tim-Trio; Siemens, 40 transverse slices, voxel size $= 3 \times 3 \times 3$ mm^3; repetition time = 2000 ms; echo time = 50 ms, field of view = 192) and continuous EEG data recorded at 5 kHz from 62 scalp sites (Easycap electrode cap) using MR-compatible amplifiers (BrainAmp MR and Brain Vision Recorder software; Brain Products). Two additional electrodes (EOG and ECG) were placed under the right eye and on the collarbone. Impedances were kept under 10 kΩ and EEG was time-locked with the scanner clock. A 7 min anatomical T1-weighted magnetization-prepared rapid acquisition gradient echo sequence (176 slices, field of view = 256, voxel size = $1 \times 1 \times 1$ mm) was acquired at the end of scanning.

fMRI preprocessing. We used statistical parametric mapping (SPM5,
AQ: D Wellcome Department of Imaging Neuroscience, London, UK; www.fil.ion.ucl.ac.uk) for image preprocessing (realignment, coregistration with the structural image, segmentation and normalization to Montreal Neurological Institute stereotactic space and reslicing to $2 \times 2 \times 2$ mm, spatial smoothing with a 6 mm full-width half-maximum isotropic Gaussian kernel for single subject as well as group analyses) and estimation of general linear models (GLMs).

fMRI intrinsic functional connectivity. For calculation of ICNs seed regions were defined as the (subject-specific) gray-matter voxels in a sphere of 10 mm radius around peaks extracted from previous studies; right intraparietal sulcus [27 −58 49] for the dorsal attention system (Fox
AQ: E et al., 2006) and dACC [0 15 40] for the intrinsic alertness system [centered between [6 15 42] and [−6 15 39] as found in intrinsic connectivity analysis by Sadaghiani et al. (2009)]. For each seed region the high-pass filtered (1/128 Hz) signal time course was averaged across all respective voxels and used as a regressor of interest in a separate GLM. Nuisance covariates of no interest included the global signal of three separate brain compartments (all white-matter voxels, all gray-matter voxels and all CSF voxels), all out-of-brain voxels as well as 6 head-motion parameters. Contrast images corresponding to the seed regressor were created for each subject and entered into a second level one-sample t test. Maps were rendered onto an inflated canonical average brain (FreeSurfer, CorTech, http://surfer.nmr.mgh.harvard.edu).

For the tonic alertness and dorsal attention ICNs as well as their individual constituent regions, BOLD time courses were extracted (group-level contrast, $p < 0.01$ family-wise error (FWE)-corrected, extent >150 voxels) for regression analysis with spectrally resolved EEG power time courses (see below). Insula, thalamus and basal ganglia constituted a large cluster and were thus separated by masking with corresponding anatomical masks generated by PickAtlas (Wake Forest University School of Medicine, http://www.fmri.wfubmc.edu/cms/software). Cortical regions were further restricted to the subject-specific intrinsic connectivity maps (first-level, $p < 0.005$ uncorrected, extent >50 voxels) and gray-matter mask.

EEG preprocessing. We used EEGlab v.7 (http://sccn.ucsd.edu/eeglab) and the FMRIB plug-in (http://users.fmrib.ox.ac.uk/~rami/fmribplugin) for gradient and pulse artifact subtraction. In two subjects, one of three rest sessions each was excluded due to insufficient EEG quality. The data were subsequently downsampled to 250 Hz and re-referenced to a common average reference. The original reference electrode was recalculated as FCz, yielding a total of 63 EEG channels.

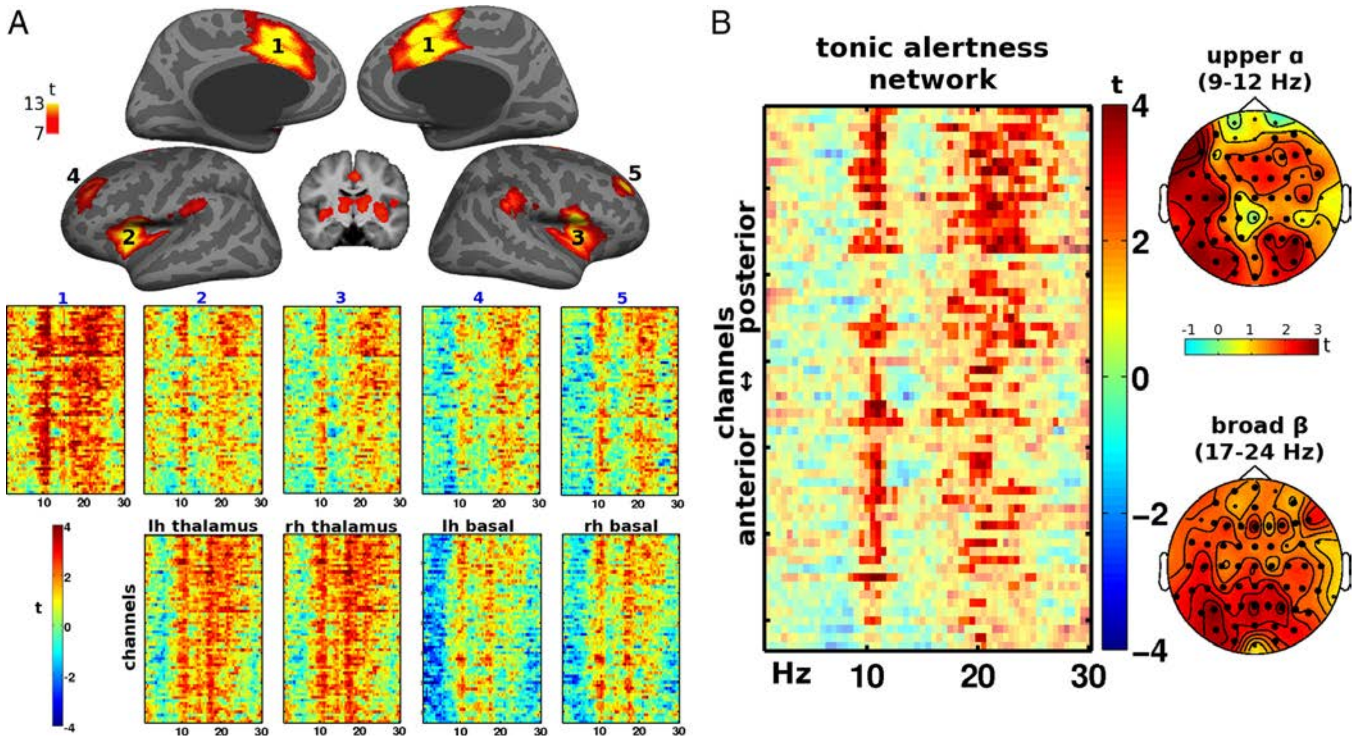
Network-based correlation analysis with the EEG power spectrum. Time-frequency analysis was computed in Fieldtrip (Donders Institute for Brain Cognition and Behavior; http://www.ru.nl/fcdonders/fieldtrip). The time-frequency analysis of power for the regression of regional fMRI signal onto EEG was performed for all the frequencies up to 30 Hz in steps of 0.5 Hz. For this we used a multitaper approach (Mitra and Pesaran, 1999) integrating the power between 1 Hz below and 1 Hz above the center frequency, and over a 2 s time-interval. This estimate was repeated for every 0.4 s. The power time courses were converted to z-scores. As artifact rejection strategy, z-scores larger than 4 were removed from the time-series. The remaining values were again z-transformed.

For each channel-frequency combination a separate design matrix was constructed, that included the hemodynamic response function (HRF)-convolved power time course for that specific channel-frequency combination. We included signal of three separate brain compartments (all white-matter voxels, all gray-matter voxels and all CSF voxels), of all out-of-brain voxels and of the motion parameters as nuisance covariates. This yielded for each frequency channel point a beta value for the EEG power regressor, which was tested at group level using a single sample t test against zero. This analysis was repeated for the fMRI time course of the tonic alertness and dorsal attention ICNs as well as each constituent region.

For the signals extracted from the entire ICNs, multiple-comparison correction was performed using a cluster-based randomization procedure (Maris and Oostenveld, 2007). This effectively controls the Type-1 error rate in a situation involving multiple comparisons. The procedure allows for the use of user defined test statistics tailored to the effect of interest within the framework of a cluster-based randomization test. Here, we used a single sample t test against zero, giving uncorrected p-values. All data points that did not exceed the preset significance level of $p < 0.05$ were zeroed. Clusters of adjacent non-zero channel-frequency points were computed, and for each cluster a cluster-level test statistic was calculated by taking the sum of all the individual t-statistics within that cluster. This statistic was entered in the cluster-based randomization procedure. For each randomization the lowest negative and highest positive cluster-sum entered a reference distribution. Clusters that fell within the extreme 2.5% of the negative and positive randomization distribution were labeled as significant. In this case, 1000 randomizations were used to compute the reference distribution. Channels separated by <4 cm were labeled as being adjacent channels. Channel positions were recorded for each subject. From these data the average distances over subjects between channel pairs were computed.

Whole-brain fMRI analysis using band-limited EEG-regressors. Power estimation for the fMRI whole-brain analysis probing BOLD signal correlation with band-specific EEG power fluctuations was based on a Hanning tapered FFT on 2 s windows, resulting in a 0.5 Hz resolution in the power spectrum. Power for each time-point was subsequently averaged over all channels. Upper alpha band was defined using the physiological criterion of individual alpha peak frequency as an anchor and 2 Hz width as suggested by Klimesch (1999). The peak was determined as the peak power value between 8 and 12 Hz after removing a 1/frequency trend from the spectrum. The global power time course of upper alpha (from individual peak bin included to 1.5 Hz above peak) and beta (15–25 Hz excluding the main residual gradient artifact frequency of 20 Hz ± 0.5 Hz) were used for regression analyses.

The power time courses were converted to z-scores. As artifact rejection strategy, z-scores larger than 4 were removed from the time-series. The remaining values were again z-transformed.



AQ: G **Figure 1.** Channel-frequency spectra for the tonic alertness network. The tonic alertness ICN was defined by applying a seed in dACC (***A***). fMRI signal time courses extracted from this network were used for regression analyses with EEG power fluctuations across the spectrum of 1–30 Hz. For all spectra, the *x*-axis represents EEG frequency, and EEG-channels are organized on the *y*-axis from top to bottom in a posterior-to-anterior order. Consistent across all individual regions (***A***) and for the entire network (***B***), positive correlations arise rather selectively in the high alpha band and more broadly in the beta band. Effects occur rather globally across the majority of EEG-channels and are furthermore characterized by distributed topographies for the network (***B***). ***A***, The ICN is defined at $p < 0.01$ FWE-corrected, extent >150 voxels, mapped on a canonical average inflated cortical surface and a coronal section [$y = -12$]. The individual cortical regions' spectra are numbered as depicted on the rendered ICN. Spectra for subcortical areas are titled respectively. ***B***, The translucent mask represents significance after correction. Bold closed channels in the topographies are part of the significant cluster.

The GFP time courses of upper alpha and beta bands were entered each into a separate GLM as a parametrically modulated regressor with stick functions modeling the event duration. Hereby, the power time courses were convolved with the canonical HRF function. Again, signal of three separate brain compartments (all white-matter voxels, all gray-matter voxels and all CSF voxels), of all out-of-brain voxels and of the motion parameters served as nuisance covariates. Contrast images corresponding to the parametric regressor were created for each subject and entered into a second level one-sample *t* test. An auxiliary uncorrected threshold of $p < 0.005$ and extent >100 voxels was used. Exceptions where a higher threshold was used for more fine-grained analysis are stated explicitly. Cluster-level corrected results are reported at $p < 0.05$ corrected threshold.

Results

To define the intrinsic connectivity network putatively related to tonic alertness we applied a seed region in the dACC. As in earlier studies (Dosenbach et al., 2007; Seeley et al., 2007; Sadaghiani et al., 2009) this resting state functional connectivity network contained bilateral insula, dACC, anterior prefrontal cortex (aPFC), thalamus and basal ganglia. We extracted the fMRI signal time course of this network as well as of its individual constituent regions and performed regression onto EEG power fluctuations F1 across the spectrum of 1–30 Hz (Fig. 1). Positive correlations with the BOLD time course occurred rather selectively in the high alpha band (~10 Hz and above; cf. individual alpha peak frequency ≈10 Hz) and more broadly in the beta band (~17–24 Hz). This effect was expressed in the spectral patterns of all constituent regions (Fig. 1*A*) and was significant in the network (Fig. 1*B*). Conversely, these correlations did not appear to be constrained to subsets of electrodes but occurred rather globally across the majority of EEG-channels. This global character was further confirmed in distributed effects on topography maps (Fig. 1*B*). The channel-frequency spectra for the network are presented in supplemental Figure 1 (available at www.jneurosci.org as supplemental material) for all 26 individual subjects. The spectral distribution of correlation of ICN activity with EEG oscillations is in accord with previously described EEG signatures of alertness in the alpha and beta range (Townsend and Johnson, 1979; Gath et al., 1983; Belyavin and Wright, 1987; Makeig and Inlow, 1993; Makeig and Jung, 1995; Haig and Gordon, 1998; Lockley et al., 2006).

For comparison, we next mapped in our data set a different ICN, the dorsal attention system, by applying a seed in right IPS and confirmed it to contain bilateral IPS, frontal eye fields and middle temporal motion-sensitive cortex (MT+) (Fig. 2*A*). F2 Again, the equivalent analysis was conducted by performing regression analyses with the spectral EEG data and the BOLD time course of the dorsal attention network and its individual constituent regions. This analysis revealed a selective negative correlation in the alpha and beta bands in all constituent regions (Fig. 2*A*) as well as the network (Fig. 2*B*). The negative correlations occurred in a broader frequency range and with a lower center frequency (~7–10 Hz) compared with the positive correlations of high alpha observed in the intrinsic alertness network. The negative beta correlations occurred in a more confined and lower frequency band (~15–18 Hz) compared with the broad positive beta correlations of the tonic alertness network.

To address the topographic specificity of our network-based correlations with the EEG spectrum, we next used band-specific

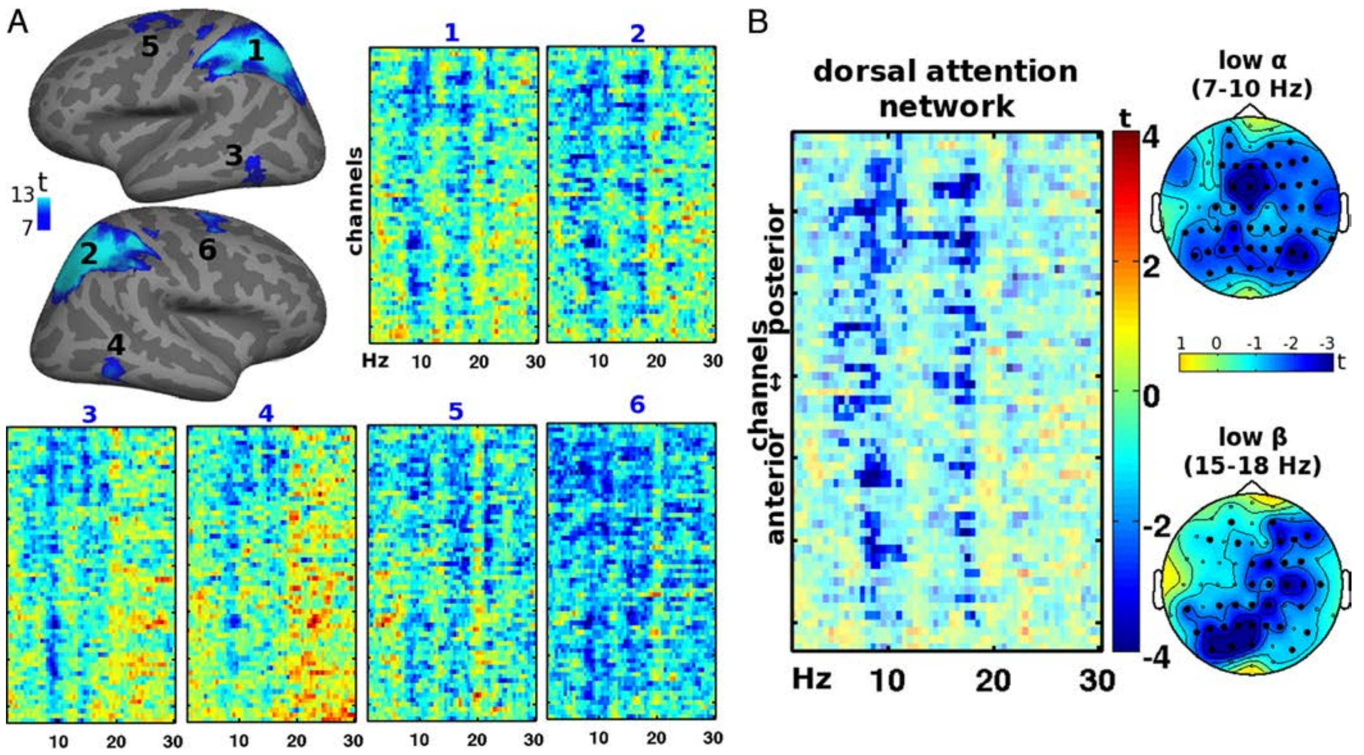


Figure 2. Channel-frequency spectra for the dorsal attention network. Dorsal attention ICN was defined by applying a seed in right IPS (***A***). fMRI signal time courses extracted from this network were used for regression analyses with EEG power fluctuations across the spectrum of 1–30 Hz. Correlations arise exclusively negatively in lower alpha and beta bands consistently across all regions of the network (***A***) and for BOLD signal averaged across the entire network (***B***). Thresholding and visualization equivalent to Figure 1.

EEG regressors to map correlations with local fMRI signal across the whole-brain volume. The previously described spectral correlation with the tonic alertness system highlighted an effect in the so-called upper alpha band, a range that has also been linked to cognitive control and performance in previous EEG studies (Klimesch, 1999; Klimesch et al., 2007). We targeted for EEG-correlated fMRI analyses an upper 2 Hz band of alpha frequency with a lower-bound anchor on individually determined peak frequency (on average 9.77 Hz ± 0.74). We tested where in the brain GFP fluctuations in the upper alpha frequency correlate positively with neural activity fluctuations as measured by BOLD signal.

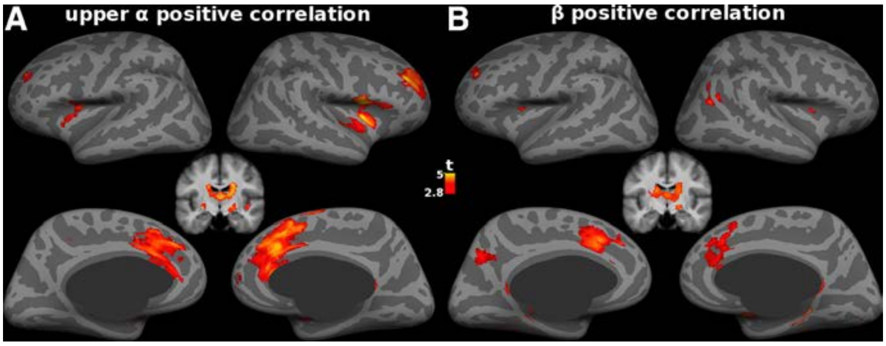


Figure 3. Positive correlation of activity with the global field power of oscillations in the alpha and beta bands. ***A***, Positive correlations with upper alpha band power arise selectively within regions of the tonic alertness network including dACC, right anterior insula, right aPFC, thalamus and basal ganglia. ***B***, Positive correlations with beta band power occur in some regions of the intrinsic alertness network, notably dACC and subcortical areas. $p < 0.005$ uncorrected, extent >100 voxels, mapped on a canonical average inflated cortical surface and a coronal section [$y = -12$].

The results of the whole-brain correlation with GFP of upper alpha are shown in Figure 3*A*. Positive correlations with the BOLD signal displayed a spatial pattern that strongly overlaps with the separately defined tonic alertness network (cf. Fig. 1*A*). These effects reached significance (cluster-level corrected, auxiliary uncorrected $p < 0.001$) in dACC ([2, 22, 40], $p < 0.001$, *z*-score 3.96, 801 voxels), a subcortical cluster bilaterally including thalamus and caudate nucleus ($p < 0.001$, *z*-score up to 4.69, 1531 voxels; caudate: [6, 24, 4], [−20 −22 24]; thalamus: [−2 −8 12], [2 −14 12]), right anterior insula ([42, 8, 6], $p = 0.003$, *z*-score 4.36, 243 voxels) and right aPFC ([34, 42, 22], $p = 0.004$, *z*-score 4.09, 228 voxels). Further correlation with upper alpha band activity was observed in the cerebellum ([26, −38, −30], $p = 0.028$, *z*-score 4.58, 150 voxels; and [−24, −74, −24], $p < 0.001$, *z*-score 4.37, 2096 voxels). Given previous concurrent EEG and fMRI studies including our own that have emphasized interindividual variability (Gonçalves et al., 2006; Laufs et al., 2006), we illustrate the homogeneity of the established effect across subjects in supplemental Figure 2 (available at www.jneurosci.org as supplemental material).

Given the aforementioned EEG studies also linking beta band oscillations to sustained performance (Townsend and Johnson, 1979; Belyavin and Wright, 1987) we next performed analogous analyses with EEG time courses from that frequency band. Global beta power (15–25 Hz) positively correlated with some areas of the intrinsic alertness network (Fig. 3*B*). These effects were weaker in size and extent than those observed for the correlations with upper alpha and achieved significance only in dACC ([−12, 22, 34], $p < 0.001$, *z*-score 3.68, 804 voxels) and a large bilateral subcortical cluster including thalamus and caudate ($p < 0.001$,

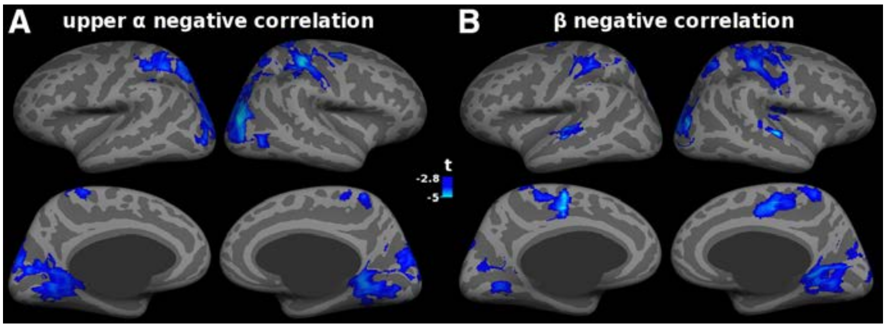


Figure 4. Negative correlation of activity with the global field power of oscillations in the alpha and beta bands. ***A***, Negative correlations with upper alpha band power occur in the dorsal attention network and visual cortex, especially dorsal visual areas. ***B***, Negative correlations with beta band power are observed in right extrafoveal and dorsal visual cortex as well as sensorimotor areas. Thresholding and visualization equivalent to Figure 3.

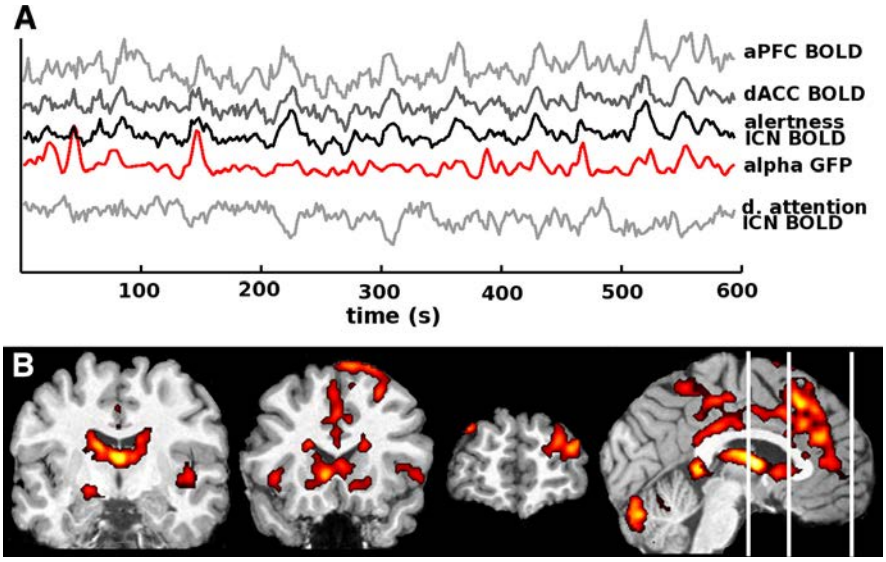


Figure 5. Signal time courses and voxelwise mapping of the correlation to upper alpha power for an individual subject. ***A***, Concurrent EEG and BOLD signal time courses for a session of 10 min. Red: The GFP time course of the individual upper alpha band after convolution with the canonical HRF. Black/gray, Raw BOLD signal time course for the tonic alertness ICN and two of its individual regions (aPFC and dACC) as well as the dorsal attention ICN as labeled. The global gray-matter BOLD signal was subtracted from these traces. The regions correspond to those visualized on the cortical surface in Figure 1*A* and Figure 2*A*, respectively. ***B***, Voxelwise mapping of the correlation to upper alpha visualized on the subject's structural image. Positive correlations with upper alpha band power arise among others in dACC, right and left anterior insula, right and left aPFC, thalamus and caudate. This first-level effect corresponds to the group-level analysis in Figure 3*A*. White lines on the sagittal view indicate the position of the three coronal slices ($y = -10$, 16 and 56, respectively). $p < 0.005$ uncorrected, extent >100 voxels.

z-score up to 4.05, 3342 voxels; caudate: [−20, −46, 18], [26 6 12]; thalamus [0 −16 16], [−2 −6 10]) as well as in the cerebellum ($p < 0.001$, *z*-score up to 4.97, 7340 voxels).

We also probed negative correlations with upper alpha band activity and obtained a spatial pattern of fMRI signal fluctuations that includes the dorsal attention system but also areas belonging to the visual system, especially dorsal areas (Fig. 4*A*). In accord with previous related studies (Goldman et al., 2002; Moosmann et al., 2003; Laufs et al., 2006), these effects reached significance (cluster-level corrected, auxiliary uncorrected $p < 0.001$) in right and left dorsal visual cortex ([38, −82, 16], $p < 0.001$, *z*-score 4.15, 752 voxels; and [−30, −88, 18], $p = 0.02$, *z*-score 3.54, 165 voxels), right superior parietal lobe ([46, −28, 58], $p < 0.001$, *z*-score 4.03, 409 voxels), left intraparietal sulcus (IPS; [−28, −64, 62], $p = 0.02$, *z*-score 3.67, 156 voxels) and extrastriate visual areas of bilateral lingual gyri ([22, −50, 0], $p = 0.005$, *z*-score 3.61, 218 voxels; and [−14, −62, 6], $p = 0.037$, *z*-score 3.44, 141 voxels). For the beta band, negative correlations were found in right, most dominantly dorsal, visual cortex ([36, −82, 14], $p < 0.001$, *z*-score 3.92, 2509 voxels), as well as in sensorimotor areas (Yuan et al., 2010) including bilateral mesial motor area ([−12, −10, 48], $p < 0.001$, *z*-score 4.19, 933 voxels) and right and left sensorimotor cortex ([50, −32, 58], $p < 0.001$, *z*-score 3.71, 2500 voxels; and [−46, −36, 62], $p < 0.001$, *z*-score 3.76, 864 voxels).

A comprehensive illustration of the effects in an individual representative subject is provided in Figure 5 by plotting for a single session time courses of upper alpha GFP and BOLD signal from different networks and regions. The HRF-convolved GFP time course in the upper alpha band shows similar fluctuations as the raw BOLD signal time course of the tonic alertness ICN as well as two of its constituent regions. Conversely, the BOLD signal time course of the dorsal attention ICN displays negative correspondence to the alpha GFP fluctuations (Fig. 5*A*). The first-level voxelwise mapping of the correlation between BOLD signal and upper alpha GFP delineates the anatomical pattern corresponding to the tonic alertness network (Fig. 5*B*).

In summary, GFP in the alpha and beta EEG frequency bands showed anatomically selective correlation with fMRI signal fluctuations in the tonic alertness system. Finally, we sought to corroborate our functional interpretation of the cingulo-insular-thalamic network in a dataset acquired in an earlier paradigm setting (Sadaghiani et al., 2009). We used the network defined through positive correlation with alpha power (Fig. 3*A*) as a spatial mask to extract peristimulus time courses of the previous activation study. We hypothesized that if the system as defined here by EEG correlation underpinned tonic alertness then it should show the same prestimulus effects as previously found for the cingulo-insular-thalamic ICN. Indeed, successful detection of the auditory stimulus compared with misses was preceded by significantly higher prestimulus activity levels in those areas where activity correlates with upper alpha band power (Fig. 6*A*; at $t = 0$ s, $t_{(10)} = 3.37$, $p = 0.007$, paired 2-tailed *t* test) and hence closely matched previous results for the related ICN (Fig. 6*B*, $t_{(10)} = 3.86$, $p < 0.005$).

Discussion

Spontaneous fluctuations of ongoing brain activity can be observed across a wide range of states, from sleep and even sedation, anesthesia, and coma over resting wakefulness all the way to effortful mental activity (Fox and Raichle, 2007). The fluctuations are spatially organized into ICNs. Their spatial patterns remain qualitatively robust across the different states but show fine-grained quantitative changes of connectivity (Horovitz et al.,

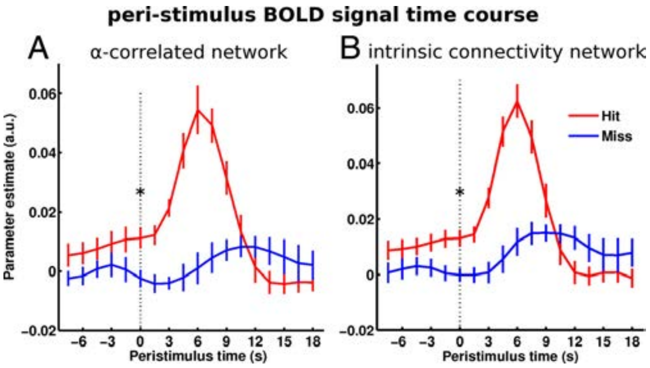


Figure 6. BOLD signal time courses of the tonic alertness system during an auditory detection task. Time courses correspond to successful detection (hit) or miss of repeated identical, near-threshold auditory stimuli (earlier study by Sadaghiani et al., 2009). ***A***, ***B***, Time courses were extracted from the network as defined by positive correlation to upper alpha band power in the current study (***A***) (cf. Fig. 3*A*) or by resting state functional connectivity in the subject group of the auditory experiment (***B***). The network defined by positive correlations to alpha shows the same effect as previously observed for the tonic alertness ICN; hits are preceded by significantly higher prestimulus baseline activity compared with miss trials. Note that the spatial pattern of the network as defined by positive alpha correlations was sufficiently robust to be applied as a mask in a different subject group. $^*p < 0.01$; dashed line indicates stimulus onset.

2009; Vanhaudenhuyse et al., 2010). EEG has a longstanding tradition in monitoring and actually defining different brain states but it has also recently been shown to reflect activity fluctuations occurring within a given state as resting wakefulness. Activity in different ICNs, as recorded for instance in resting state fMRI studies, has been tied to power in different EEG frequency bands or even patterns of power across the EEG spectrum (Mantini et al., 2007). Here, we have pursued a hypothesis derived from previous work and focused on slow activity fluctuations in an as of yet anatomically and functionally insufficiently characterized ICN comprising dACC, anterior insula, thalamus and aPFC (Dosenbach et al., 2007; Seeley et al., 2007). Due to typical coactivation of this network with lateral parietal and prefrontal control regions during paradigm settings, it has stayed elusive whether or not these systems form a unitary or rather two distinct functional networks (cf. Dosenbach et al., 2008 vs Vincent et al., 2008). We show that fluctuations in concurrently recorded electroencephalographic indices of tonic alertness are associated with slow activity fluctuations in the cingulo-insular-thalamic network. This result hence further supports a functional distinction of this network from other control regions.

The most consistent previously reported EEG-hallmark of sustained alertness is the power of alpha oscillations. In a series of experiments, Makeig and colleagues found that lapses in behavioral performance were accompanied by decreases in near 10 Hz ongoing alpha power (Makeig and Inlow, 1993; Makeig and Jung, 1995). Similarly, Dockree et al. (2007) found sustained levels of near 10 Hz alpha to reflect tonic maintenance of attentional resources associated with enhancement of phasic goal-directed processing. Likewise, increased alpha phase synchrony (Haig and Gordon, 1998) and power (Gath et al., 1983) have been associated with shorter reaction times in oddball tasks. And sustained increases in upper alpha power correlate with shorter reaction times, less lapses in stimulus detection, and negatively with subjective sleepiness ratings (Lockley et al., 2006). While some of the above findings were obtained in eyes open condition, others were established with closed eyes, indicating that the positive relation between enhanced alpha oscillations and performance is consistent across both conditions. In the present study, we found a positive correlation of GFP in the upper alpha (and to some extent beta) band with activity in the cingulo-insular-thalamic network.

Our findings are overall in accord with results across several previous studies although no single study has so far established the correlation that we show here, namely between alpha band power and an ICN. Positive correlation with alpha band activity has previously been reported for the thalamus (Goldman et al., 2002; Moosmann et al., 2003; de Munck et al., 2007; Ben-Simon et al., 2008; Difrancesco et al., 2008), insula (Goldman et al., 2002) and dACC (Difrancesco et al., 2008). Apart from higher power in our study due to a large study group, differences in the findings may be due to the fact that previous work focused on posterior rather than global alpha and collapsed over lower and upper alpha frequencies.

The correlation of activity in the cingulo-insular-thalamic system with upper alpha band oscillations as the most robust electroencephalographic marker of vigilance fluctuations suggests that this system could serve a role in maintaining tonic alertness. We found similar albeit weaker evidence for beta oscillations that have also been linked to performance in settings requiring sustained alertness (Townsend and Johnson, 1979; Belyavin and Wright, 1987).

As previous related studies discussed above, our analyses were conducted on data recorded during rest where no stimuli or task requirements interfere with the ongoing activity fluctuations that manifest in EEG and fMRI. This advantage for the purpose of our study comes at the price of including no direct measure of perceptual performance in the same dataset. However, the functional interpretation of our findings is supported by previous functional imaging studies that explicitly manipulated tonic alertness and found associated effects in an anatomically very similar network (Sturm and Willmes, 2001; Sturm et al., 2004). Despite qualitative similarity of those latter findings, the present ICN mapping and the network defined by alpha power correlation, this evidence remains indirect. To further validate our conclusions, we hence analyzed fMRI signal time courses in the EEG-defined network but in another subject group previously performing a perceptual experiment requiring tonic alertness (Sadaghiani et al., 2009). Notwithstanding structural intersubject variability between the two study groups, we found that activity in the network linked to upper alpha band power improved perceptual performance with higher prestimulus signal preceding hits compared with misses. This observation further corroborates a close functional correspondence between the cingulo-insular-thalamic ICN, upper alpha band power and tonic alertness.

Tonic alertness refers to a sustained function that is distinct from arousal on the one hand and selective attention on the other hand (Posner, 2008). While arousal (in the sense of wakefulness and responsiveness) is subject to very slow (e.g., circadian) and constitutive modulations and is controlled by the brainstem (Jones, 2008), attention transiently ensures selective local processing of specific features and is tightly linked to activity in dorsolateral parietofrontal cortices (Driver and Frackowiak, 2001). In contradistinction to these cognitive functions, tonic alertness refers to an intermediate capacity that expresses nonselective readiness for perception and action implemented by a cortico-subcortical system (Sturm and Willmes, 2001). The anatomy and function of the cingulo-insular-thalamic network is well suited to underpin this control process. The nonspecific thalamic nuclei project very broadly throughout the cortex, qualifying for general functions such as alerting (Scheibel and Scheibel, 1967). Among these, the anterior thalamic nucleus projects massively to the dACC, a major cognitive control region implementing performance monitoring and adaptive top-down control (MacDonald et al., 2000; Kerns et al., 2004). Anterior insula with its reciprocal connections to the limbic system and ACC constitutes an anatomical and functional connection hub between extended networks (Sporns et al., 2007; Sterzer and Kleinschmidt, 2010), and has been suggested to dynamically control the switching between internally and externally oriented mental activity (Sridharan et al., 2008).

But apart from the shared correlation with tonic alertness what is the relation between this network and global alpha band power? Note that our findings do not imply the cingulo-insular-thalamic network as a generator but rather as a modulator of power in alpha oscillations across the cortex such that this transpires into a GFP signal. Anatomically, thalamo-cortico-thalamic feedback connections are the basis by which the thalamic component of this network might provide an efficient way for controlling global cortical expression of alpha oscillations (Lopes da Silva et al., 1980). Alpha oscillations were the first distinct pattern of ongoing brain activity described in human EEG but their functional significance remains debated. Historically, the Berger effect of alpha disruption by eye opening (Berger, 1929) was taken as indication that this was an “idling” rhythm of the awake but unoccupied resting brain (Pfurtscheller et al., 1996). Apparently in line with this notion, the allocation of selective spatial attention is associated with reductions in alpha activity spatiotopically corresponding to attended locations and enhanced stimulus processing (Rihs et al., 2007). Indeed, we confirmed negative correlations of alpha power with activity in regions related to the control of selective attention, conforming to earlier studies (Laufs et al., 2003).

If interpreted in terms of tonic alertness, our data are nonetheless congruent with an active role for alpha oscillations. We propose that alertness involves a generalized ‘windshield wiper’ mechanism and that alpha oscillations serve this purpose by rhythmically and synchronously clearing the flood of sensory information on a rapid time scale to reduce distraction and hence enhance detection of novel and relevant sensory information. This proposed mechanism is compatible with evidence of alpha synchronization as an active mechanism for inhibitory top-down control (Klimesch et al., 2007). Enhanced alpha synchronization has been reported in active suppression of task-irrelevant cortical regions in diverse contexts including intermodal selective attention tasks (Foxe et al., 1998), retinotopically specific distractor suppression (Worden et al., 2000; Kelly et al., 2006), feature-selective visual working memory tasks (Jokisch and Jensen, 2007), lateralized somatosensory working memory tasks (Haegens et al., 2010) and go/no-go suppression of learned motor sequences (Hummel et al., 2002). In a hierarchical view of attentional function we therefore suggest that both alertness and selective attention serve increased sensitivity but deploy antagonistic mechanisms: Due to its nonselectivity alertness involves what amounts to a suppression and selective attention a specific and focal disruption of this global effect. This view is in accord with the interpretation of alpha desynchronization as a gradual release of inhibition (Klimesch et al., 2007).

The majority of experimental paradigms require the conjunction of alertness and selective attention due to the use of prespecified targets. These settings therefore do not permit to clearly disentangle the contributions from these two attentional functions. For instance, it is not clear whether the expression of alpha oscillations could also be selective and specifically target processes with a high potential for distracting from the task at hand. We propose that a global mechanism is ecologically more useful because not all functional contexts will permit to sharply tune prior assumptions in terms of what to expect as relevant and what as distracting. This question, however, will require future dedicated experiments that orthogonalize the requirements for alertness and selective attention. Some preliminary evidence can be seen in the fact that in our previous study with a nonspatial auditory detection task, there was an antagonistic influence of two usually conjointly task-positive systems on perceptual performance, facilitation by alertness and deterioration by selective spatial attention (Sadaghiani et al., 2009).

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Supplementary material

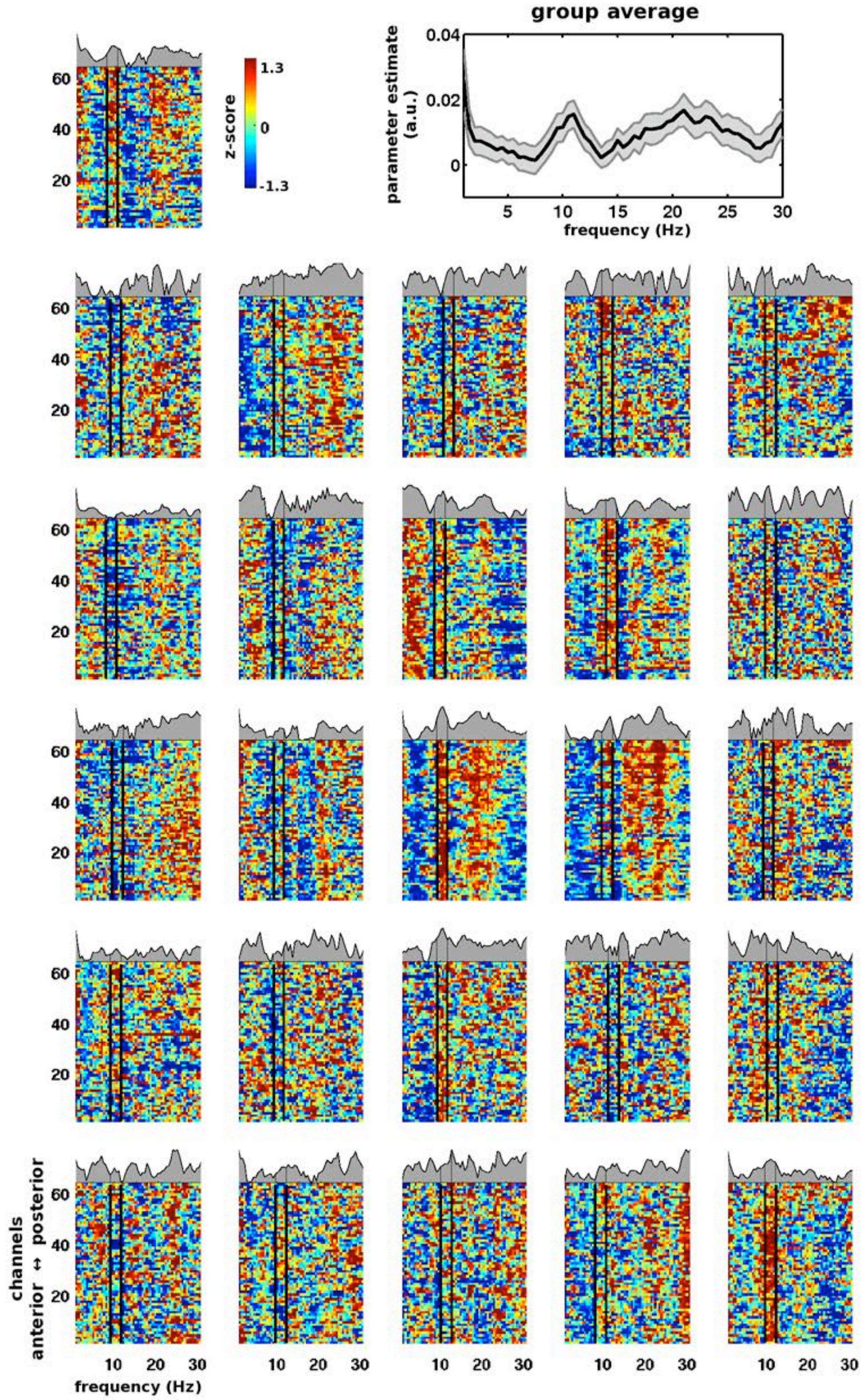
Figure S1

Channel-frequency spectra for the tonic alertness network for all individual subjects. The 26 spectra constitute the parameter estimates that entered the group-level t-test presented in Figure 1B. For each subject, the parameter estimates were z-transformed across the channel-frequency spectrum and the color scale corresponds to z-score = -1.3 to 1.3. The x-axis represents EEG frequency (1-30 Hz), and EEG-channels are organized on the y-axis from top to bottom in a posterior-to-anterior order. Given the relatively homogeneous effect across the majority of channels, we also provide the across-channel average of the (non-z-transformed) parameter estimates on top of each subject's spectrum. The large, upper right plot shows the corresponding result pooled across all subjects; the grey zone corresponds to SEM across subjects. Note the clear peak in the upper alpha band in the group result.

Figure S2

Upper alpha global field power correlation with the tonic alertness network. For all individual subjects the plot shows the parameter estimates averaged across all voxels of the alertness network as defined by correlation with upper alpha band global field power. This network corresponds to Figure 3A with the general procedure and thresholding specified in the methods section except that so as to avoid any bias from partial circularity, we determined each individual's score in a network that was defined by a second level analysis on the other 25 subjects (by estimating 26 random effects models in a rotating leave-one-out procedure). We then computed the average parameter estimate for the network in the 26th subject we had left out in that analysis. The plot shows the parameter estimates for individual subjects reordered by magnitude. The effect shows a fairly homogenous unimodal distribution across subjects that is clearly distinct from zero.

Figure S1


group average
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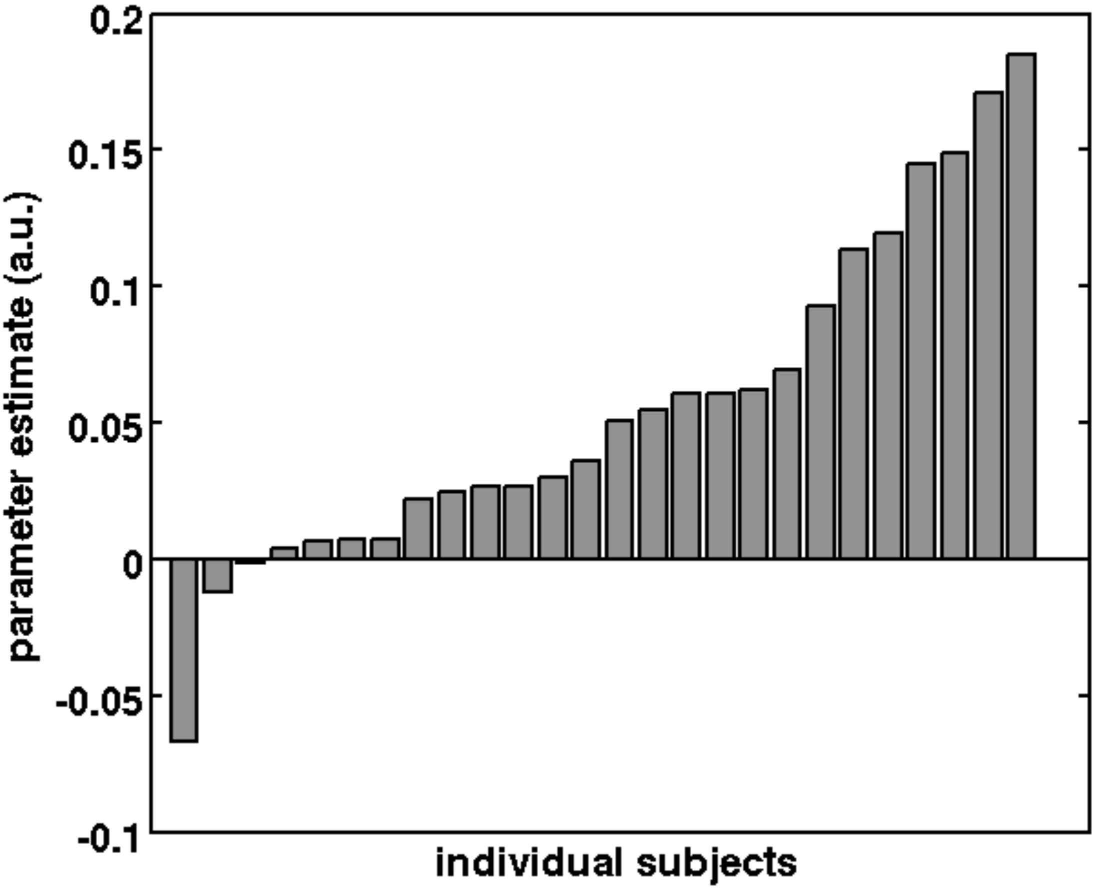
frequency (Hz)

Figure S2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parameter estimate (a.u.)
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Predictive Coding or Evidence Accumulation? False Inference and Neuronal Fluctuations

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Abstract

Perceptual decisions can be made when sensory input affords an inference about what generated that input. Here, we report findings from two independent perceptual experiments conducted during functional magnetic resonance imaging (fMRI) with a sparse event-related design. The first experiment, in the visual modality, involved forced-choice discrimination of coherence in random dot kinematograms that contained either subliminal or periliminal motion coherence. The second experiment, in the auditory domain, involved free response detection of (non-semantic) near-threshold acoustic stimuli. We analysed fluctuations in ongoing neural activity, as indexed by fMRI, and found that neuronal activity in sensory areas (extrastriate visual and early auditory cortex) biases perceptual decisions towards correct inference and not towards a specific percept. Hits (detection of near-threshold stimuli) were preceded by significantly higher activity than both misses of identical stimuli or false alarms, in which percepts arise in the absence of appropriate sensory input. In accord with predictive coding models and the free-energy principle, this observation suggests that cortical activity in sensory brain areas reflects the precision of prediction errors and not just the sensory evidence or prediction errors *per se*.

Citation: Hesselmann G, Sadaghiani S, Friston KJ, Kleinschmidt A (2010) Predictive Coding or Evidence Accumulation? False Inference and Neuronal Fluctuations. PLoS ONE 5(3): e9926. doi:10.1371/journal.pone.0009926

Editor: Jan Lauwereyns, Kyushu University, Japan

Received November 25, 2009; **Accepted** March 9, 2010; **Published** March 29, 2010

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Funding: This fMRI experiment was part of a general research program on functional neuroimaging of the human brain which was sponsored by the Atomic Energy Commission (principal investigator Denis Le Bihan). This work was funded by the Agence Nationale de la Recherche (SPONTACT; France). S.S. is supported by the Friedrich-Ebert Foundation (Germany). G.H. is supported by a Minerva fellowship (Max Planck Society). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

The notion that perception involves inference dates back for centuries and has been refined using mathematical models, grounded mostly in a Bayesian framework [1]. Yet, contemporary models of perceptual decisions differ in terms of neuronal implementation, and the neurophysiological evidence garnered in their support [2,3]. In some accounts, cortical activity reflects sensory evidence that is accumulated to a critical level to yield a perceptual decision. This family of diffusion or race models can be regarded as dynamic extensions of signal detection theory [4]. In these models, the implicit neuronal code is a log-probability or likelihood-ratio code. In other hierarchical models, cortical activity encodes top-down predictions and bottom-up prediction error [5,6]. The error signal is accumulated and used to optimise predictions and suppress prediction error or free-energy. In this case, inference rests on predictions that serve to explain away the difference between predicted and incoming sensory information.

Both views are supported by studies of evoked cortical responses during perceptual decisions [7,8,9]. However, it is difficult to say which model better explains empirical observations, because both can be formulated to give similar predictions. Recently, it has been shown that ongoing cortical activity, prior to sensory stimulation, can predict subsequent perceptual decisions [10,11,12,13]. As ongoing activity fluctuates between trials, so does the perception of identical stimuli. Critically, the two theoretical accounts make qualitatively different predictions about the relationship between ongoing activity and perception. Put simply, under evidence accumulation models, activity increases with the evidence for a stimulus, whereas under predictive coding it reflects the precision of the prediction error [14]. Therefore, in evidence accumulation models, high ongoing activity will bias inference to detection with (true hits) or without (false alarms) an appropriate stimulus. Conversely, under predictive coding, ongoing activity levels in sensory cortex reflect the precision (inverse variance) of sensory noise. When sensory noise is low prediction errors are amplified. If sensory noise is high, this induces self-inhibition among units coding prediction error and leads to a relative increase in the influence of top-down predictions [14]. In this setting, false alarms are emitted when the precision is too low to counter top-down predictions for which there is no sensory evidence.

In short, accumulation models suggest high ongoing activity will bias towards stimulus detection (true hits or false alarms). Conversely, the predictive coding or free-energy formulation suggests that high ongoing activity (i.e., precise prediction errors) will bias towards correct inference (hits or correct rejections). This means we can adjudicate between the two models by examining pre-stimulus activity for hits, correct rejections, false alarms and misses.

Here, we report functional magnetic resonance imaging findings related to false alarms in two perceptual paradigms. Findings from both experiments have been reported previously but only with respect to hits and misses (where we had greater trial numbers) [12,13]. However, these two conditions alone do not permit any conclusion regarding the nature of the signal, prediction error or sensory evidence. We therefore conducted a new analysis that included those subjects in the two experiments with a sufficient number of false alarms for statistical analysis. We obtained small but significant effects that were consistent across both experiments and that suggest that neural activity in sensory areas codes the precision of prediction error.

Results

The first experiment involved detecting motion coherence in random dot kinematograms with coherent motion at threshold (periliminal) in most trials and above or below threshold (supra- and subliminal) in a smaller number of trials [12]. We measured cortical activity, prior to evoked responses (grey ellipse in Fig. 1), in the human visual motion complex V5/hMT+. According to accumulation models we should observe pre-stimulus activity levels for: hits and false alarms > misses and correct rejections. And, according to predictive coding: correct rejections and hits > misses and false alarms. Our empirical observations confirmed the latter (Fig. 1).

The greatest difference in pre-stimulus activity was between the correct rejections and false alarms (solid blue and red lines, respectively). This is clear evidence that pre-stimulus activity reflects the precision (predictive coding) of the subsequent percept not its content (evidence accumulation). More formally, an ANOVA of the differences across activity at time points 0 and 1.5 s showed a main effect of accuracy, correct vs. incorrect ($p < .022$, consistent with predictive coding), but no main effect of percept, coherent vs. incoherent (predicted by accumulation). In *post-hoc* t-tests, pre-stimulus activity in subsequent hit-trials was significantly greater than misses; and activity in false alarms were significantly less than in correct rejects ($p = .048$ and $p = .031$, respectively, unpaired one-sided t-tests; on a qualitative level, "hit>miss" in 8/9 subjects and "correct rejection>false alarm" in 6/9). The use of one-sided *post-hoc* t-tests was justified by the directed assumptions of the two models that we considered; accumulation vs. prediction. It should be pointed out that these effects were not significant when just testing activity in a single epoch (0 or 1.5 s) as in our previous analyses of hits and misses alone. This observation indicates a loss of statistical power relative to previous analyses that included a greater number of subjects [12].

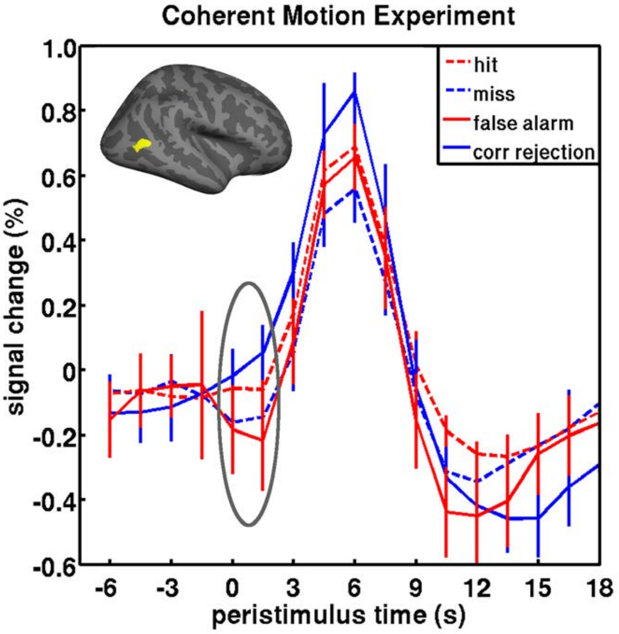

Figure 1. Peristimulus fMRI signal time-courses from the visual motion experiment. Data were normalized to grand mean and averaged across 9 subjects (bars represent standard error of the mean) performing a motion coherence judgment task. The insert specifies the conditions as a function of stimulus and percept. The inflated right hemisphere rendering of the group result shows the right hMT+ region of interest, which was identified subject by subject in a localizer procedure employing coherent motion stimuli vs. static displays. The grey ellipse covers the pre-stimulus period submitted to statistical testing (see main text).

doi:10.1371/journal.pone.0009926.g001

To determine the topographic specificity of the observed effects, we analyzed BOLD time courses in a set of control regions that were robustly activated or deactivated by the motion task. These regions included areas involved in early visual motion processing (V1/V2), as well as attention and perceptual decision making (right IPL, right and left FEF, right IFG, and ACC). No region showed the "hit>miss" or "correct rejection>false alarm" effects in the pre-stimulus baseline, and subsequent voxel-based whole brain analyses were also negative.

In the second experiment, we studied detection of auditory signals presented at threshold against ongoing scanner noise [13]. This detection paradigm can be reconciled with the form of the previous experiment by regarding it as a continuous discrimination, with two alternatives of stimulus 'present' or 'absent'. However, this free-response paradigm does not furnish correct rejection trials (i.e., subjects are not required to indicate the stimulus is absent). We expected the difference between hits and false alarms to be even more pronounced than in the first experiment. This is because in the auditory fMRI experiment ongoing sensory noise levels were higher due to scanner noise than in the visual experiment, where inter-stimulus intervals contained a stationary dot pattern. Under predictive coding, this higher sensory noise should suppress the gain of error units and reduce activity levels, accentuating the effect of endogenous fluctuations.

As before, the predictions of the two theoretical accounts differ: Evidence accumulation would expect hits and false alarms (i.e., an auditory percept) to follow higher baseline levels, relative to misses (no percept). Conversely, the predictive coding account suggests that (incorrect) misses and false alarms are foreshadowed by significantly lower activity than (correct) hits. Our findings in this experiment supported the latter prediction (Fig. 2). False inference (false alarms - red solid lines, and misses - blue dashed lines) were preceded by significantly lower levels of activity in auditory cortex than veridical hits (red dashed line, $p = .021$ and $p = .018$, respectively, in unpaired one-sided t-tests; on a qualitative level, "hit>miss" in 7/9 subjects and "hit>false alarm" in 7/9). There was no significant difference in activity preceding misses vs. false alarms. This low activity prior to false alarms is consistent with a scheme that under-weights sensory evidence via an inhibition of error units and thus fails to constrain top-down predictions. The profound activity dip in the 3 s preceding a false alarm could indicate a critical level of ongoing activity that is necessary for the endogenous generation of a percept, in the absence of the stimulus. Conversely, in the case of misses, it is the dwindling of a prediction (or the toggling to the alternative prediction) and the associated

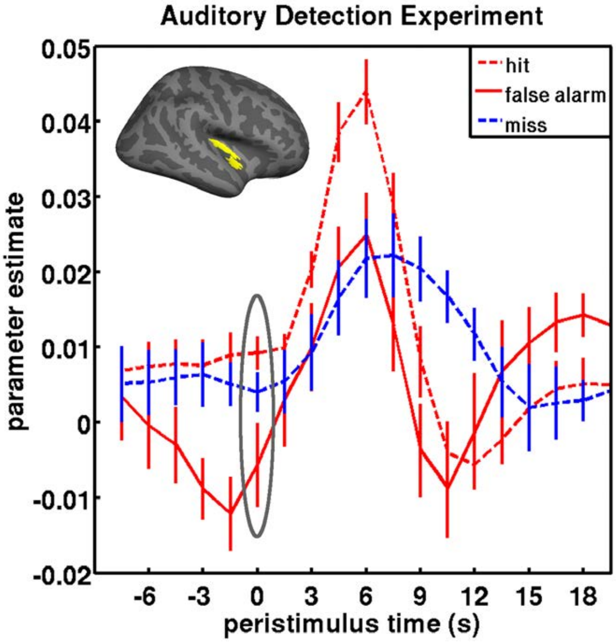

Figure 2. Peristimulus fMRI signal time-courses from the auditory experiment. Data were estimated under a finite response model and averaged across 9 subjects (bars represent standard error of the mean) performing an auditory stimulus detection task. Data are plotted for conditions specified by an insert. The inflated right hemisphere rendering of the group result shows the location of the region of interest, which includes early auditory cortex with parts of Heschl's gyrus (identified bilaterally subject by subject). The grey ellipse covers the pre-stimulus period submitted to statistical testing (see main text).
doi:10.1371/journal.pone.0009926.g002

increase in the noise estimation for top down influences that via self-inhibition down-regulates the local fMRI signal such that despite sensory input no percept is reported.

In contrast to our local findings in the motion experiment, the pre-stimulus effects in the auditory experiment appeared to be much less spatially confined. Similar to the original publication–where we report distributed "hit>miss" and "miss>hit" effects -, maps (at t = 0 s) of "hit>false alarm" show a number of regions outside of auditory cortex, including mid-cingulate cortex, polar and ventro-medial prefrontal cortex and early visual cortex (cluster-level $p<0.05$, corrected, after auxiliary $p<0.005$, uncorrected). The reverse contrast "false alarm>hit" yielded no significant foci ($p<0.05$, uncorrected). Note that such a difference between the experiments was to be expected because the auditory paradigm involved detection of near-threshold stimuli in a free-response setting instead of two-alternative forced choice decisions on ambiguous but clearly notable stimulation in the motion experiment.

In both experiments, we found no relationship between the duration of the prior SOA and behavioural outcome. In the motion experiment, the SOAs were 29.2±0.8 s for hits, 30.3±0.9 s for misses, 29.6±1.3 s for correct rejections, and 30.1±3.2 s for false alarms (mean ± sd). In the auditory experiment, the SOAs were 30.6±0.2 s for hits, and 30.4±0.4 s for misses. False alarms occurred 17.8±1.1 s after the preceding stimulus, i.e. approximately in the middle between two auditory stimuli.

Discussion

Both experiments support an interpretation of neural activity (indexed by fMRI signal) in specialized sensory cortical regions as coding prediction error and not evidence or log-probability (cf. classical signal detection theory). Our analyses were conducted using the responses of brain regions that are specialised for the sensory information required for the subjects' perceptual decisions. Our findings therefore cannot be compared with those obtained in higher order (polymodal) cortex like the lateral intra-parietal and premotor areas. However, our findings can be compared to studies of sensory cortex, where baseline variations were removed [7].

In terms of neuronal computation, the free-energy principle encompasses evidence accumulation schemes as a special case that is manifest at higher levels in the sensory hierarchies, as prediction error is accumulated to optimise high-level representations and the ensuing top-down predictions of sensory input [15]. The evidence we present here in favour of the free-energy principle comes from sensory regions and from the analysis of perceptual outcome as a function of activity prior to stimulation. Our analysis was constrained to pre-stimulus windows, because this avoids the confounding effect of evoked signal changes (e.g., differences in sensory stimulus properties and their frequency as well as their perception and behavioural consequences). Yet, the same principle is likely to hold throughout the entire time series of neural activity. For instance, the evoked responses in the first experiment show a main effect of stimulus type with greater responses to incoherent motion stimuli. Again, this argues against a coding of sensory evidence and in favour of a coding of the greater "surprise" associated with the less frequent incoherent motion stimuli, compared to the more frequent periliminal coherent motion stimuli. It is also obvious from our findings that widely applied analysis features such as baseline normalisation to pre-stimulus signal may distort effects observed in the evoked responses.

Our study departs from usual treatments of neuroimaging results in terms of predictive coding [16] because we did not look for the correlates of prediction error; we tried to disambiguate between evidence accumulation and predictive coding schemes. This means we had to dissociate the effects of precision and prediction error *per se* (which are conflated during the expression of precision-weighted prediction error). We therefore focussed on pre-stimulus activity levels, which can only reflect putative changes in the precision that is conferred on prediction errors, when they are later induced by a stimulus.

An important limitation of our analyses is that functional neuroimaging, while useful in recording population synaptic activity, does not resolve the fast dynamics underpinning perceptual decisions. This limitation is tempered by previous functional neuroimaging studies, where fluctuations in ongoing activity can predict subsequent percepts on a trial by trial basis [11,12,13]. In other words, we can exploit fluctuations in neuronal activity and subsequent perceptual processing to establish causal relationships through temporal precedence, even with slow hemodynamic signals. As in previous studies, we analysed time segments of the signal that are as close to the upcoming stimulus as possible without including stimulus-driven responses We refer to the peri-stimulus fMRI responses until stimulus onset as 'pre-stimulus'. However, because the hemodynamic response delays and disperses underlying neuronal activity, some 'pre-stimulus' neuronal activity will actually appear after stimulus onset in the fMRI time-series. Happily, the converse situation (post-stimulus neuronal activity confounding pre-stimulus fMRI data) cannot occur. We suppose that the fluctuations in baseline activity we recorded with fMRI reflect endogenous (ongoing) fluctuations in fast neuronal activity. Indeed, computational studies suggest that fast synchronised activity fluctuates in power with the characteristic ultra-slow frequencies seen in fMRI [17]. Furthermore, the general picture from combined EEG and fMRI studies [18] suggests that increases in fast oscillatory activity elevate BOLD signals. These slow modulations of fast activity are, we presume, mediated by neuromodulatory effects at a synaptic level. These effects underlie changes in post-synaptic gain of the sort associated with attention [19] and perceptual precision (i.e., signal to noise) [20].

Our findings illustrate that pre-stimulus fMRI signals cannot be interpreted as encoding sensory evidence but are consistent with an alternative explanation that it reflects the level of attention. Indeed, attention modulates cortical activity in sensory areas even in the absence of input [21]. This interpretation is not at odds with an account grounded in the free-energy principle, because the increased precision that may be reflected in higher levels of endogenous activity is thought to mediate the effects of directed attention [15]. This means that the optimization of precision in predictive coding and attention become the same thing. Whether this necessarily applies to our observations is a complicated issue. An effect of fluctuations on directed (endogenous) attention should fulfil more criteria than mere modulation of local signal in a sensory area. Among these are associated effects in higher order attentional control centres, increased sensory response amplitudes and shortened reaction times. No such evidence was found in our first experiment [12] and only partial support in the second experiment, where attention and awareness are not easily dissociated in response amplitudes and where reaction times are only available for hits [13]. Conversely, the insufficient evidence for an attention account does not invalidate the interpretation along the lines of the more general free-energy principle. In short, whatever the neural or cognitive origin of endogenous fluctuations, their impact on perceptual performance is captured by predictive coding models. This is an important conclusion because the functional role of such ongoing or endogenous activity fluctuations, which have traditionally been neglected in many neurophysiological and theoretical investigations of perceptual inference and decisions, is becoming increasingly evident [22,23,24,25].

Materials and Methods

Ethics Statement

Both studies received ethics committee approval by the authorities responsible for our institution (INSERM-CEA, NeuroSpin). All subjects gave written informed consent.

Data acquisition and pre-processing

Details of both experiments have been published previously [12,13]. Imaging data for both studies were acquired on a 3T MRI scanner (Tim Trio, Siemens, Erlangen). Functional imaging used a T2*-weighted gradient-echo, echo-planar imaging sequence (25 slices, TR = 1500 ms, TE = 30 ms, FOV 192, voxel size 3×3×3 mm, inter-slice gap 20%). Anatomical imaging used a T1-weighted MPRAGE sequence (160 slices, TR = 2300 ms, TE = 2.98 ms, FOV 256, voxel size 1.0×1.0×1.1 mm for the motion experiment, and 176 slices, TR = 2300 ms, TE = 4.18 ms, FOV 256, voxel size 1×1×1 mm for the auditory experiment). We used SPM5 (http://www.fil.ion.ucl.ac.uk, Wellcome Trust Centre for Neuroimaging, London, UK) for image pre-processing that involved realignment, coregistration, normalization to MNI stereotactic space, spatial smoothing with an isotropic Gaussian kernel of 6 and 12 mm (motion experiment) or 5 and 6 mm (auditory experiment) full-width-half-maximum for single subject and group analyses, respectively and estimation of general linear models.

Motion experiment

Twelve right-handed subjects with normal or corrected-to-normal visual acuity (6 female, ages 19–30) participated in the motion experiment. Stimuli were dynamic dot displays of 500 white squares (size 0.2°) randomly distributed on a dark grey annulus (23°). Subjects were instructed to maintain gaze within a central blue rectangle (1°) surrounded by a light grey circular patch (3°) throughout the experimental sessions. For 355 ms intervals, stimuli moved up- or downwards, at 14°/s and with variable motion coherence. Subjects were asked to report as quickly and accurately as possible by button presses after each stimulus whether they had perceived coherent or random motion. Prior to scanning we determined individual motion coherence thresholds based on the method of constant stimuli (average motion coherence threshold across subjects 13%, range 8 to 20%). During fMRI scanning, three motion coherence levels were used: subliminal (1% coherence, 20 trials), periliminal (individual threshold, 60 trials), and supraliminal (30% coherence, 20 trials). Stimuli were presented in two 25 minute runs with 50 trials each. Between stimuli, the display was static for inter-stimulus intervals (ISI) of 20 to 40 s that were randomly selected from a uniform distribution.

Functional images for two 1000 volume experimental runs and one 208 volume localizer run were acquired. Localizer fMRI runs identified cortical regions sensitive to two types of coherent visual motion, up- or downwards motion and an expanding 'starfield'. Continuous 16 s motion blocks were separated by 10 s stationary periods, and each condition was repeated over 6 blocks in counter-balanced order. Motion-sensitive areas were identified by mapping for each subject the contrast 'motion > stationary' at $p<0.001$, uncorrected. A local maximum near the ascending limb of the inferior temporal sulcus was defined as hMT+ (see original publication for coordinates). After removing session effects and linear trends from the BOLD signal time series of the main experiment, we extracted the percent signal change time courses of all periliminal and subliminal trials from 4 scans (6 s) before to 12 scans (18 s) after target onset and sorted them according to hits (perceiving periliminal stimuli as coherent), misses (periliminal stimuli as random), correct rejections (subliminal stimuli as random), and false alarms (subliminal stimuli as coherent). Here, we only report data from those subjects who generated a sufficient number of false alarms (n = 9 out of 12 subjects). Across subjects, near-threshold stimuli generated 57% hits and 43% misses, and subliminal stimuli 74% correct rejects and 26% false alarms.

Auditory experiment

Twelve right-handed normal hearing subjects (2 female; ages 19–30) participated in the auditory experiment. One subject reported to have fallen asleep in one session and was thus excluded from analysis. Subjects were exposed to sparse near-threshold auditory stimuli and performed an auditory detection task. The stimulus was a 500 ms noise burst with its frequency band modulated at 2 Hz (from white noise to a narrower band of 0–5 kHz and back to white noise). Subjects were blindfolded and instructed to report as quickly and accurately as possible by a right hand key press whenever they heard the target sound despite scanner's background noise. In a first 6.5 min fMRI run, which was not analyzed, we determined each subject's auditory threshold using a simple staircase procedure with 25 trials and inter-stimulus intervals randomized between 2.5 and 5 s. Next, each subject performed 2 and some subjects 3 experimental runs of 20 min duration. In each run, target stimuli were presented at individual threshold (periliminal stimuli) on 36 trials and at a fixed supra-threshold level on 4 'catch' trials. ISIs ranged unpredictably from 20 to 40 s, with each specific ISI used only once. Before each run, the target stimulus was played a few times at supra-threshold volume for (re)memorization and subjects were informed that in most of the trials the target sound would be played at a barely perceptible level. If within 1.5 s of stimulus onset a key was pressed this trial was counted as a hit, if not as a miss. All other key presses were classified as false alarms. Here, we restricted our analysis to those subjects who generated at least 5 false alarms (n = 9 out of 11). These subjects detected 59±17% of the near-threshold stimuli.

Experimental runs consisted of 820 volumes. An additional passive localizer run for defining auditory responsive brain regions was acquired after the main experiment. This 81 volume run consisted of three 20 s-blocks of repetitive stimulus presentation with 0.5 s inter-stimulus intervals (ISI) at clearly audible volume separated by 15 s baseline epochs. Voxels responding to the auditory stimulus were defined on a subject-by subject basis in two steps. First, at the group level the contrast periliminal stimuli (i.e. hits and misses) > baseline ($p<0.001$) was masked by the passive auditory localizer contrast at $p<0.001$. A spherical search space of 10 mm was defined around the peak of the peri-Heschl clusters with the highest z-score. Next, for each subject's corresponding first-level contrast all voxels within this search space were selected that passed a lenient threshold ($p<0.05$, uncorrected).

As false alarms occurred at unpredictable times and sometimes prior to hemodynamic relaxation, we could not directly analyze fMRI signal time courses as in the motion experiment. We hence used a finite impulse response (FIR) model on the high-pass filtered data with very low cutoff (1/1000 Hz) and no pre-whitening to ensure linear drift removal while minimizing interference with low frequency brain activity fluctuations. The FIR model used 24 peristimulus stick functions (x 1.5 s bins) for each of the four conditions, hits, misses, false alarms and catch trials. For near-threshold stimuli (hits and misses) time-locking was based on stimulus presentation; for false alarms it was based on behavioural reports minus the subject's average reaction time in hit trials (794±109 ms).

Author Contributions

Conceived and designed the experiments: GH SS AK. Performed the experiments: GH SS. Analyzed the data: GH SS. Wrote the paper: GH SS KJF AK.

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The Relation of Ongoing Brain Activity, Evoked Neural Responses, and Cognition.

frontiers in
SYSTEMS NEUROSCIENCE

REVIEW ARTICLE
published: 23 June 2010
doi: 10.3389/fnsys.2010.00020

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 (Horovitz 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 (Horovitz 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 visuomotor 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

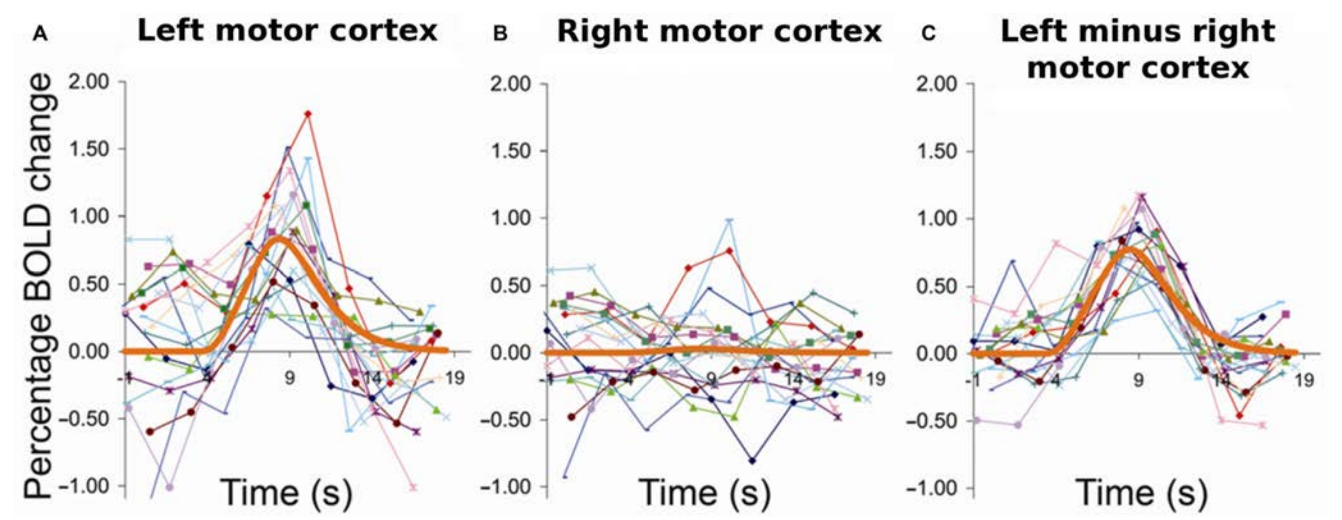

FIGURE 1 | Ongoing activity fluctuations account for variability in trial-to-trial evoked responses. Subjects pressed a response button with their right hand at long intervals (>14 s) in response to visual indication. **(A)** Left, i.e., task-invoked motor cortex; **(B)** right motor cortex; **(C)** left motor cortex after removal of activity from right motor cortex. Each curve corresponds to the raw time course of one trial for the same individual subject. The thick orange line represents the respective best-fit gamma function. The event-related activity in left motor cortex showed high trial-to-trial variability. Strong variability was likewise observed in the spontaneous activity in the other, i.e., right hemisphere and could account for a major portion of variance of the left hemispheric evoked responses on a trial-by-trial basis. Reprinted from Fox et al. (2006a) with permission from Nature Publishing Group.

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

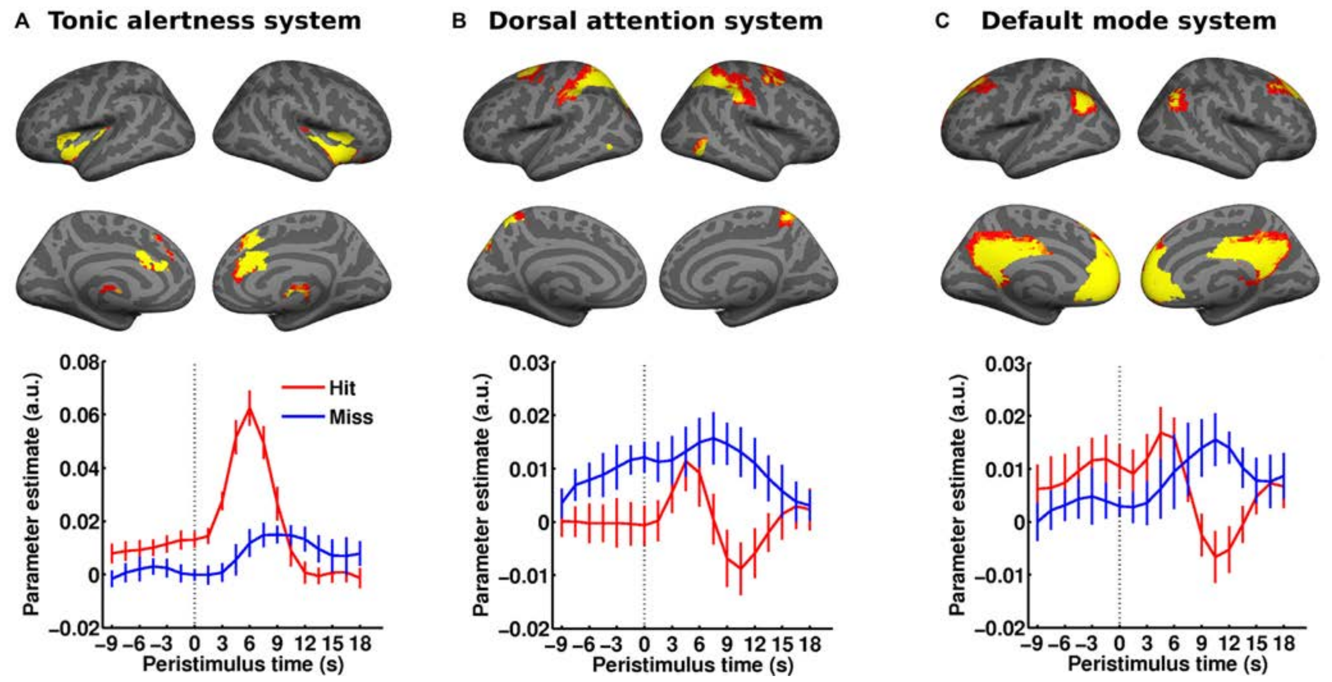

FIGURE 2 | Distributed ongoing activity fluctuations in large-scale ICNs impact perceptual performance. (A–C) Subjects performed a free-response auditory detection task (cf. **Figure 3A**). The pre-stimulus BOLD signal (dotted vertical line marking stimulus onset) from three ICNs (rendered on a canonical inflated cortical surface) was examined as a function of perceptual outcome. Hits were preceded by significantly higher pre-stimulus activity in the tonic alertness ICN **(A)** as well as the default-mode ICN **(C)** while higher pre-stimulus activity in the dorsal attention ICN **(B)** foreshadowed misses. Error bars represent standard error across subjects. Adapted with permission from Sadaghiani et al. (2009). For comparison with a somatosensory threshold detection task please cf. Figure 2 in Boly et al. (2008). This figure was not reprinted here due to fees requested by the publisher John Wiley and Sons for reprint permission.

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

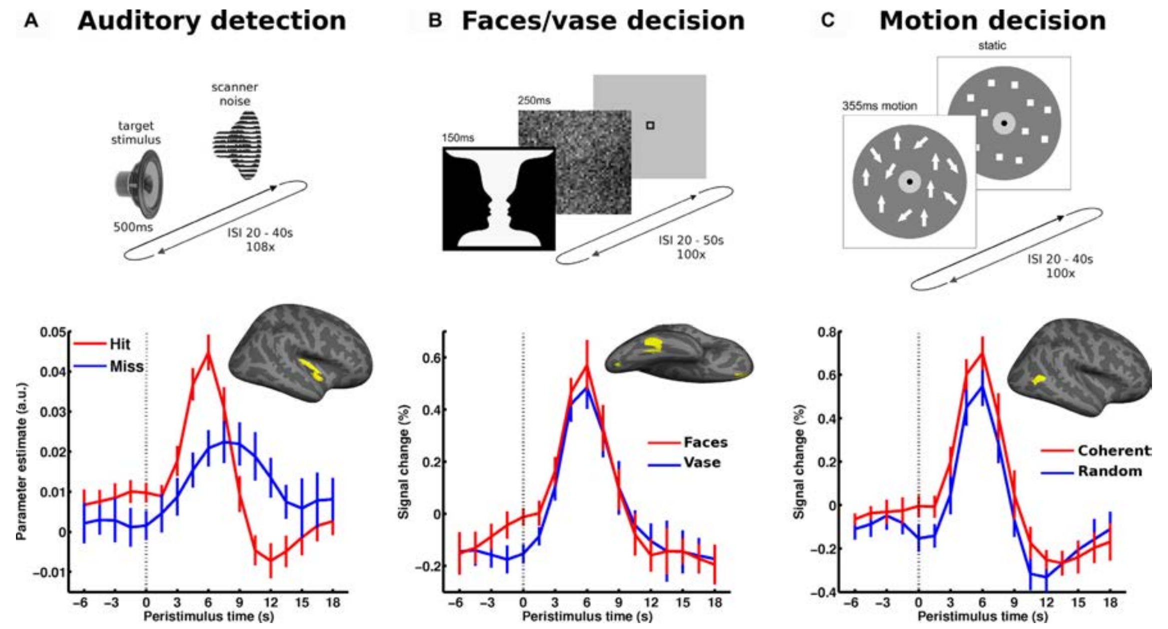

FIGURE 3 | Local spontaneous variations in ongoing activity of specialized sensory regions impact perception. The upper part illustrates the paradigm: **(A)** auditory detection experiment: in a free-response setting subjects detected an auditory target stimulus presented at perceptual threshold. **(B)** Perceptual decision on an ambiguous figure: subjects reported either faces or vase perception in response to flashes of the faces-vase ambiguous figure. **(C)** Motion decision experiment: random dot motion was presented at motion coherence threshold and subjects decided trial by trial whether motion was coherent or random. In all experiments, trials followed at long and unpredictable intervals. In each experiment, the pre-stimulus BOLD signal (dotted vertical line marking stimulus onset) was examined as a function of perceptual outcome and sampled from accordingly specialized sensory areas. The corresponding regions of interest (early auditory cortex, FFA and hMT+, respectively) are presented on a canonical inflated cortical surface of the right hemisphere. In all experiments, higher pre-stimulus time course in the respective sensory region biased towards perceiving stimulus properties for which these regions are particularly sensitive. Error bars represent standard error across subjects. For more details see Hesselmann et al. (2008a,b); Sadaghiani et al. (2009).

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 linking 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 Kisley 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

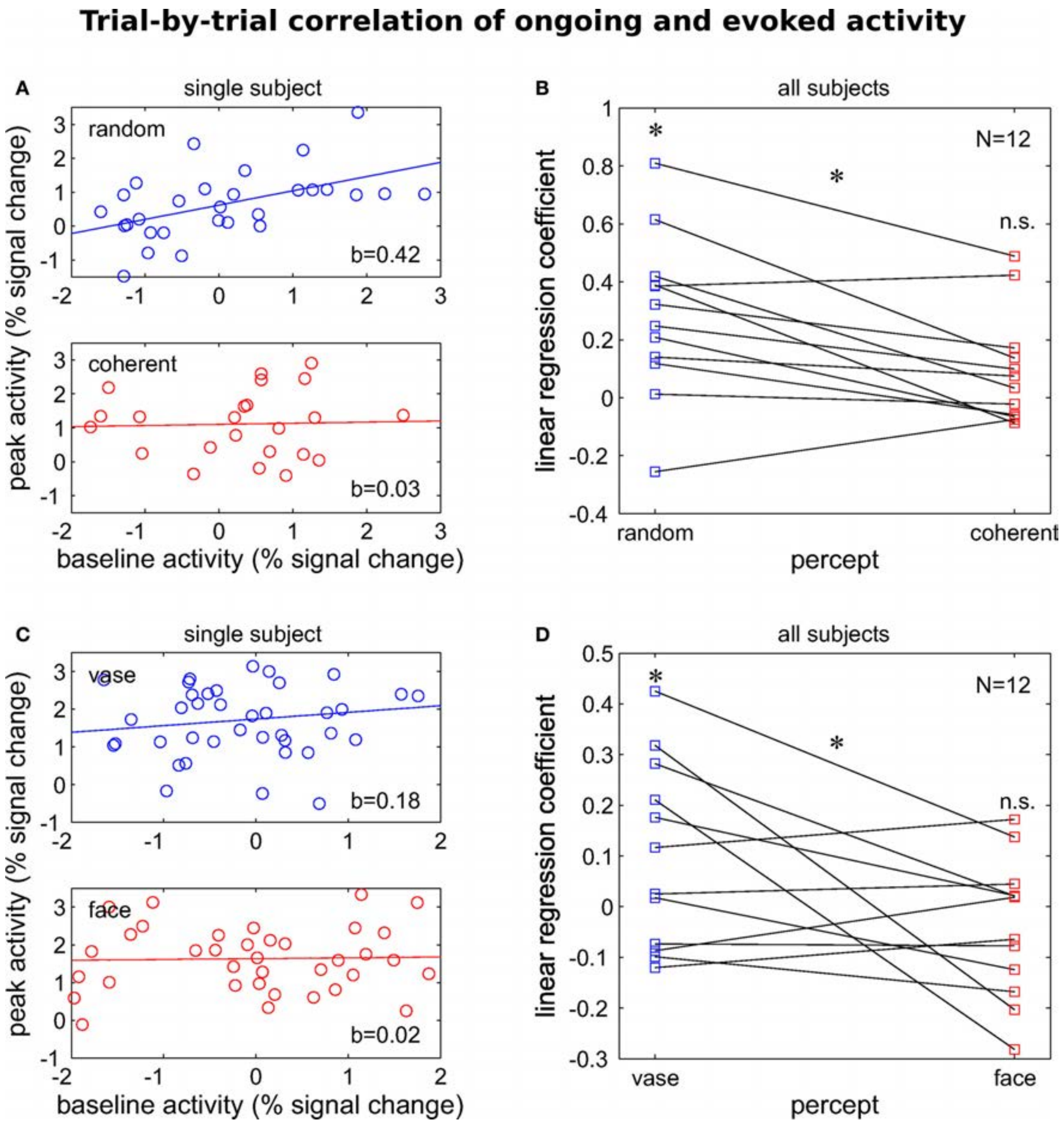

FIGURE 4 | Percept-dependent and non-linear interaction of evoked responses with pre-stimulus baseline activity. Percept-dependent linear regression was performed between trial-by-trial pre-stimulus activity at –1.5 s and peak activity at 6 s relative to stimulus onset. For two independent experiments, the regression is illustrated for one representative single subject and the regression coefficient is given for the group. **(A,B)** The motion decision experiment (for stimuli cf. **Figure 3C**): coefficients were significantly larger than 0 when motion was perceived as coherent ($t_{11} = 3.55$, $p < 0.01$) but not when it was perceived as random ($t_{11} = 1.7$, n.s.) and significantly different between the two perceptual outcomes ($t_{11} = 3.24$, $p < 0.01$, paired). Adapted with permission from Hesselmann et al. (2008a). **(C,D)** The face-vase decision experiment (cf. **Figure 3B**): likewise, coefficients showed a trend >0 when faces were perceived ($t_{11} = 1.88$, $p = 0.087$) but not when the vase was perceived ($t_{11} = –1.06$, n.s.). Importantly, they were significantly different between the two perceptual outcomes ($t_{11} = 2.31$, $p < 0.05$, paired). Dataset from Hesselmann et al. (2008b). All tests are two-sided t statistics.

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 peceptual 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.

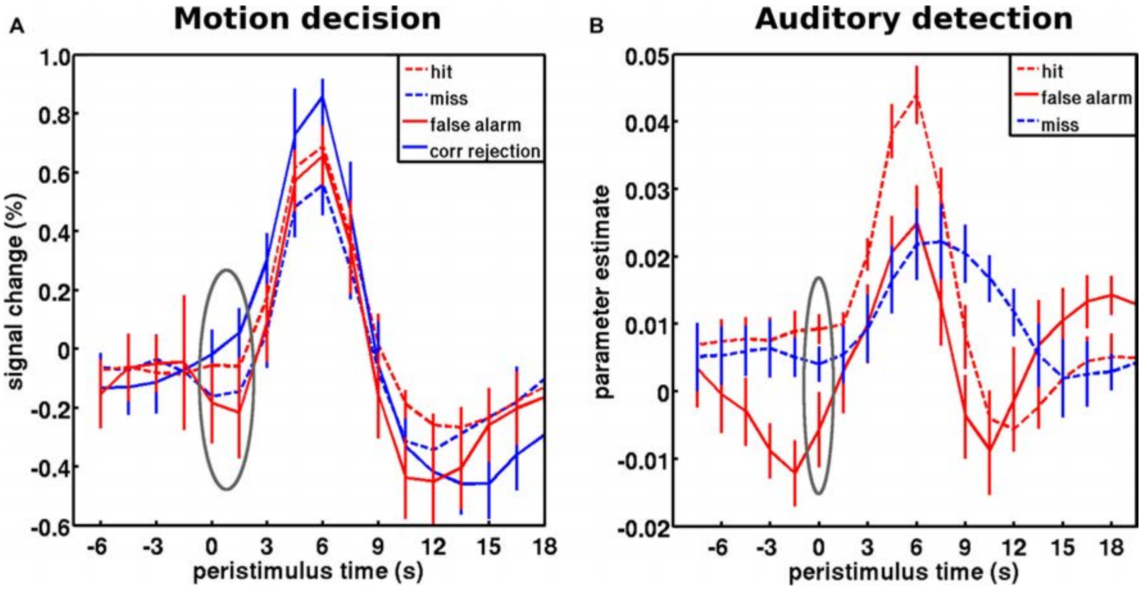

FIGURE 5 | Baseline activity levels in false vs. correct inferences are captured by the predictive coding framework. (A) Peristimulus fMRI signal time courses from the motion decision experiment: for stimuli and region of interest cf. **Figure 3C**. Hits and misses correspond to trials at threshold motion coherence level (on average 13%), while correct rejections and false alarms correspond to occasional trails with a quasi-random coherence level (1%). Pre-stimulus activity showed a main effect of accuracy, correct vs. incorrect (consistent with predictive coding), but no main effect of percept, coherent vs. incoherent (predicted by evidence accumulation). Pre-stimulus activity prior to hits was significantly greater than misses; and pre-stimulus activity in false alarms were significantly less than in correct rejects. **(B)** Peristimulus time courses from the auditory detection experiment: for stimuli and region of interest cf. **Figure 3A**. False alarms occurred occasionally when subjects reported to hear the target stimulus in the absence of stimulation. As assumed by predictive coding, false inference (false alarms and misses) were each preceded by significantly lower levels of activity in auditory cortex than veridical hits. Note that this free-response paradigm does not furnish correct rejection trials (i.e., subjects are not required to indicate the stimulus is absent). The gray ellipse covers the pre-stimulus period submitted to statistical testing. The time courses for hits and misses correspond to the respective time courses in **Figure 3**. However, note that only a subset of subjects that had a sufficient number of wrong inferences was included in this analysis. Error bars represent standard error across subjects. Adapted with permission from Hesselmann et al. (2010).

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.

It has been argued that evoked response variability is coordinated rather than arbitrary and substantiates the very essence of cognition as it translates into behavioral variability (Buzsáki, 2006). From this point of view, we reviewed evidence that ongoing brain activity fluctuations influence trial-by-trial behavior and perception of identical stimuli. Site and sign of this impact depend on cognitive context and the functional role of a given region or neuroanatomical system. This cognitive variability over time is the visible manifestation of a continuous trajectory of ongoing activity, an itinerant trajectory that can be thought of as a memory trace building up within a complex and adaptive system. Intrinsic activity hence constitutes the brain's internal context for processing external information and generating behavior (Kenet et al., 2003; Fontanini and Katz, 2008). Future progress on these issues can only be made by treating ongoing activity as a signal instead of noise and by shifting from a behaviorist stance that records evoked responses to a constructivist approach that interrogates neural history records as the substrate of a process of active perceptual synthesis.

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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3 Author's publications

- Sadaghiani S, Scheeringa R, Lehongre K, Morillon B, Giraud AL, Kleinschmidt A (2010) Intrinsic Connectivity Networks, Alpha Oscillations and Tonic Alertness: A simoultaneous EEG/fMRI Study. Journal of Neuroscience, 30(30):10243-50.
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4 Acknowledgments

First and foremost, I would like to thank my supervisor, Andreas Kleinschmidt, for the unparalleled mentoring and personal support. I'm deeply grateful to have been his PhD student and to profit from his incomparable knowledge and expertise. I was fascinated by the way Andreas applies relatively simple experimental designs to tackle very fundamental principles of brain function and cognition. He instructed me in conducting the particular research underlying this thesis, but also in always seeing the "bigger picture". He has been a patient and attentive supervisor but also a personally understanding mentor. Andreas always found the appropriate words to motivate me; an appreciated advice that he had to often remind me on was "don't panic, count to ten, then panic"...

I thank Stanislas Dehaene for responding to my interest in working in his research unit. I'm grateful for the possibility to take advantage of the scientific input and the technical and personal support of this research unit, but especially for the numerous, very inspiring personal discussions with Stan.

The manuscripts that form the basis of my thesis are the result of the collaborative effort of many colleagues. I thank Guido Hesselmann for co-writing the papers, and for his methodological help, conceptual discussions and friendship that accompanied me throughout the past three years, and that I hope to continue. I thank René Scheeringa for his indispensable input to the simultaneous EEG-fMRI study, his expertise and indefatigable patience in explaining methodological and conceptual issues to me. Very special thanks to Karl Friston for his fundamental input to the conceptual interpretation of our experimental findings and for his strong input to the respective papers. I thank Katia Lehongre, Benjamin Morillon and Anne-Lise Giraud for generously providing us with the large simultaneous EEG-fMRI dataset that are at the basis of important findings reported in the thesis. I thank Gaël Varoquaux for the very fruitful scientific discussions and for generously offering me cooperation on his paper on ICA methodology.

Many thanks to Evelyn Eger for her help in methodological questions, for her patience with my endless questions, and for her friendship that I deeply appreciate. She has been very important to me in all respects throughout the last three years.

I very much enjoyed the cooperations with Flore Baronnet and Clio Coste which I hope to continue beyond my stay at NeuroSpin.

Many thanks to all other members of the Unicog research unit at NeuroSpin for the scientific input and for the unforgettable experiences that they shared with me.

I would like to thank Kâmil Uludağ for taking the time to read and evaluate my thesis. I deeply appreciate Kâmil as a mentor of my laboratory rotation and as a wonderful friend. I thank Uta Noppeney for volunteering as a member of my thesis committee and am very grateful for her instructions in experimental design and data analysis throughout my laboratory rotation and my master studies that I could build on during my doctorate studies. Many thanks to Andreas Nieder to be a member of my thesis committee and for his encouragement.

I would like to thank Horst Herbert and Katja Deiss for their patient and indefatigable

support throughout the last 5 years.

I was supported by the Friedrich-Ebert-Stiftung, Germany, during the entire doctorate studies as well as throughout my preceding undergraduate studies. I'm very thankful for this support that made possible my doctorate studies in the laboratory of my choice and which included several stays abroad and participation in summer schools and conferences.

I thank my parents for their unconditional support that I could count on in all the ups and downs of the past years. This thesis is the result of your efforts. I love you! I thank my sisters for their love and support.

Special thanks to Nader Angha for motivational input and for the deep knowledge and hope that he has provided me with in all the past years.

Last but not least, I would like to thank my best friend Stefanie Kühn that I could always count on. You are the open ear that has always been there for me and inspired me during my thesis. I'm looking forward to many more wonderful decades of friendship with you!