Patterns of hemodynamic low-frequency oscillations in the brain are modulated by the nature of free thought during rest

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During conscious rest, the mind switches into a state of wandering. Although this rich inner experience occupies a large portion of the time spent awake, how it relates to brain activity has not been well explored. Here, we report the results of a behavioral and functional magnetic resonance imaging (fMRI) study of the continuous resting state in 307 healthy participants. The analysis focused on the relationship between the nature of inner experience and the temporal correlations computed between the low-frequency blood oxygen level-dependent (BOLD) fluctuations (0.01–0.1 Hz) of five large-scale modules. The subjects’ self-reported time spontaneously spent on visual mental imagery and/or inner language was used as the behavioral variable. Decreased temporal correlations between modules were revealed when subjects reported more time spent thinking in mental images and inner language. These changes segmented the three modules supporting inner-oriented activities from those associated with sensory-related and externally guided activities. Among the brain areas associated with inner-oriented processing, the module including the lateral parietal and frontal regions (commonly described as being engaged in the manipulation and maintenance of internal information) was implicated in the majority of these effects. The preponderance of segregation appears to be the signature of the spontaneous sequence of thoughts during rest that are not constrained by logic, causality, or even a rigorous temporal organization. In other words, though goal-directed tasks have been demonstrated to rely on specific regional integration, mind wandering can be characterized by widespread modular segregation. Overall, the present study provides evidence that modulation of spontaneous low-frequency fluctuations in the brain is at least partially explained by spontaneous conscious cognition while at rest.

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Introduction

In the absence of external goal-directed tasks, i.e., during the so-called resting state, the mind is thought to switch into a specific state called “mind wandering” (Antrobus et al., 1970). This state of “free association” is characterized by a stream of internally oriented random and spontaneous thoughts (Andreasen et al., 1995). Also referred to as daydreaming (Singer, 1966), this state has been demonstrated to occupy one-third of our time spent awake (Kane et al., 2007; Klinger and Cox, 1987) and includes all thoughts that are not involved in the processing of task stimuli (Teasdale et al., 1995). Thought-sampling techniques (Heavey and Hurlburt, 2008; Lehmann et al., 1998; Singer and Antrobus, 1970) and retrospective questionnaires (Andrews-Hanna et al., 2010; Delamillieure et al., 2010; Mazoyer et al., 2001) have revealed that this state is mostly characterized by the generation of self-related mental images and inner speech oriented towards past or future concerns. These observations have resulted in the idea that the mind is restless (Smallwood and Schooler, 2006), and some authors have even suggested that the resting state is an extremely active state during which we pursue fundamental life tasks (Baars, 2010).

At a physiological level, the human brain is responsible for approximately 20% of total energy metabolism in the body, despite comprising only about 2% of the total body mass (Clark and Sokoloff, 1999). This high level of energy consumption mainly supports synaptic activity (Shen et al., 1999; Shulman et al., 2004) and varies little between the resting state and attention-demanding or perceptual tasks (Fox and Raichle, 1986; Sokoloff et al., 1955). Moreover, functional magnetic resonance imaging (fMRI) studies have revealed
that spontaneous low-frequency fluctuations (LFFs; <0.1 Hz) in blood oxygen level-dependent (BOLD) signals can be uniformly detected in the brain in the absence of goal-directed tasks (Biswal et al., 1995; Cordes et al., 2000; Lowe et al., 1998). More recently, the electrophysiological basis of these LFFs was linked to spontaneous neuronal activity (He et al., 2008). Overall, LFFs appear to be critical to the characterization of functional organization in the resting-state brain (Salvador et al., 2005). Independent component analysis (ICA) (Hyvarinen et al., 2001) and functional connectivity analysis (Biswal et al., 1995; Friston, 1994) have consistently and reproducibly detected brain networks of regions exhibiting temporally correlated LFFs at rest (Damoiseaux et al., 2006; Shehzad et al., 2009). These so-called resting-state networks (RNs) have also been shown to be similar to networks detected during activation tasks (De Luca et al., 2005; Smith et al., 2009), which led to the hypothesis that these networks remain “active” when the brain is at rest.

An increasing number of studies have also described positive or negative temporal correlations between RNs (Fox et al., 2005; He et al., 2009; Tian et al., 2007). Positive temporal correlations may support functional specialization within distinct regions, whereas negative temporal correlations may reflect functional segregation between regions in which opposite or competing goals are being subserved (Fox et al., 2005). Consistent with these definitions, brain functional organization has been proposed to comprise two negatively, temporally correlated intrinsic and extrinsic “systems” that support two competing processes, such as internally and externally oriented cognitive processes, respectively (Fox et al., 2005; Golland et al., 2008). In this framework, we recently showed a finer division of these systems in five modules and proposed a functional model of brain activity at rest (Doucet et al., 2011). The intrinsic system was partitioned into three modules that subserved the generation of spontaneous thoughts, inner maintenance and manipulation of information, and cognitive control and switching activity. The extrinsic system was found to consist of two distinct modules: one including primary somatosensory and auditory areas and the dorsal attentional network, the other encompassing the visual areas.

How the observed spontaneous LFFs are related to cognition, and more specifically to spontaneous cognition, is a crucial question. Resting state is often used in cognitive paradigms as an explicit or implicit reference, and this phenomenon has been demonstrated to be present during goal-directed tasks (Greicius et al., 2003) and could significantly interact with the task signal (Fox et al., 2007). LFFs at rest are affected by previous learning (Lewis et al., 2009; Mazoyer et al., 2009; Waites et al., 2005) and influence the behavioral results of a subsequent task (Sadaghiani et al., 2010). Mason et al. (2007) were among the first to show that the default-mode network (Raichle et al., 2001) activity during a working memory task is related to subjects’ self-reported propensity to generate stimulus-independent thoughts. Nevertheless, during a resting state condition, the results concerning spontaneous cognition remain scarce. To the best of our knowledge, no less degree those of the extrinsic system. To the best of our knowledge, no equivalent studies have been published.

In order to take into account the large variability of both physiological and behavioral measurements, we acquired data on a large population sample: 307 healthy participants underwent a single, uninterrupted resting-state condition while being scanned with fMRI. Subjects were instructed to keep their eyes closed and to let their thoughts wander freely. Immediately following the functional acquisition, an introspective questionnaire, the Resting-State Questionnaire (ReSQ) (Delamilliere et al., 2010), was used to assess the nature of the participants’ inner experience, focusing on the two major mental activities: visual mental imagery (IMAG) and inner language (LANG). Finally, we investigated the impact of the amount of time spent by the subjects on each type of mental activity on the functional connectivity between five large-scale resting-state networks, called modules, that we previously identified (Doucet et al., 2011).

### Materials and methods

#### Participants

A total of 307 healthy young adults (mean age 26.9 years ± standard deviation [SD] 8.1 years) were scanned with fMRI for an 8-min resting-state condition. The sample was balanced for gender (152 women) and handedness (153 left-handers) (Table 1). All of the participants provided informed written consent, and the local ethical committee (CPP de Basse-Normandie, France) approved the study.

#### fMRI data acquisition

Imaging was performed on a Philips Achieva 3-Tesla MRI scanner. Spontaneous brain activity was monitored using BOLD fMRI during the resting-state for 8 min (T2*-EPI, sequence parameters: 240 volumes; TR = 2 s; TE = 35 ms; flip angle = 80°; 31 axial slices; 3.75 x 3.75 x 3.75 mm³ isotropic voxel size). Immediately before fMRI scanning, participants were instructed to “keep their eyes closed, to relax, to refrain from moving, to stay awake, and to let their thoughts come and go.” Prior to the fMRI session, structural MR brain images were acquired including a high-resolution 3D T1-weighted volume (sequence parameters: TR = 20 ms; TE = 4.6 ms; flip angle = 10°; inversion time = 800 ms; turbo field echo factor = 65; sense factor = 2; field of view = 256 x 256 x 180 mm³; 1 x 1 x 1 mm³ isotropic voxel size). T2*-weighted multi-slice images were also acquired (T2*-weighted fast field echo (T2*-FFE), sequence parameters: TR = 3500 ms; TE = 35 ms; flip angle = 90°; sense factor = 2; 70 axial slices; 2 x 2 x 2 mm³ isotropic voxel size). No cognitive training or task was realized by participants during the imaging session.

#### Table 1

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<th>Study sample demographics and behavioral data.</th>
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<tr>
<td>Demographic data</td>
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* Number of years at school and university.
Behavioral data acquisition and processing

The functional acquisition was immediately followed by a debriefing interview using the ReSQ (Delamillieure et al., 2010) to assess the subject’s spontaneous thought content. Each participant was asked to give an estimate of time spent (on a 0–100% scale) on visual mental imagery (IMAG) and inner language (LANG) during the fMRI exam. In the ReSQ, IMAG is defined as having thoughts in the shape of images, whereas LANG corresponds mainly to inner speech; i.e., talking to oneself with one's own voice without overt production, as well as auditory mental imagery, which is associated with the recall of elements of conversations spoken by oneself or others. Estimations were given twice, once at the beginning of the ReSQ and once at the end. For each individual, the mean of the two estimations was computed and considered for the following analyses.

fMRI data pre-processing

Pre-processing was performed on the basis of Statistical Parametric Mapping subroutines (SPM5, Wellcome Department of Neurology, London, UK; www.fil.ion.ucl.ac.uk/spm). For each participant, the anatomical T1-weighted volume was segmented into three brain tissue classes (grey matter, white matter (WM), and cerebrospinal fluid (CSF)) and spatially normalized using the stereotaxic space of the Montreal Neurological Institute (MNI) template (Ashburner and Friston, 2005). The fMRI data were corrected for slice timing differences and motion (6 parameters: 3 translations and 3 rotations) and registered on the T2*-FFE volume. Combining the T2*-FFE with the T1-weighted registration matrix and previously computed T1-weighted normalization matrix, fMRI data were then normalized to the MNI stereotaxic space (2×2×2 mm³ cubic voxels) and spatially smoothed (Gaussian 6 mm full width at half maximum filter). Using in-house Matlab-based software, each voxel of the image time series was motion corrected using time evolutions from the six motion parameters and cleaned of contamination by both WM and CSF signals using linear regression. For each individual, the temporal evolution of WM and CSF was estimated in regions of interest defined by the relevant individual segmented brain tissue classes. Finally, fMRI data were temporally filtered using a least square linear-phase FIR filter design band-pass (0.01–0.1 Hz).

Functional connectivity of fMRI modules

The spatial maps of five large-scale resting-state networks, called modules, were used as regions of interest. These modules were previously identified using independent component analyses. Three modules, default-mode (M1a), frontoparietotemporal (M1b) and frontal/supramarginal/subcortical (M1c), were included in the intrinsic system, and two modules, centroparietal (M2a) and occipital (M2b), were part of the extrinsic system (Doucet et al., 2011). For each participant and module, an individual BOLD fMRI time series was computed by averaging the BOLD fMRI time series of all voxels belonging to the module’s spatial map. Next, for each individual and each pair of modules we computed the Pearson’s linear correlation coefficient (r) between the module’s BOLD fMRI time series. For each pair of modules, this coefficient was declared to be significant at the group level when > 50% of the 307 individual values were larger than the threshold set at |r| > 0.18 (i.e., p < 0.05 corrected for multiple comparisons [number of module pairs]) (Doucet et al., 2011). Only module pairs with significant correlation coefficients at the group level were considered for further analysis. Individual temporal correlations were then converted to Fisher’s z correlation coefficients, called “module functional connectivity” coefficients (MFCs), for further statistical analysis.

Effects of inner experience content on module functional connectivity

Using the software program JMP 9.0.0 (2010, SAS Institute Inc.), we applied repeated-measures multivariate analysis of covariance (MANCOVA) to analyze the effects of IMAG, LANG, and their interaction (IMAG LANG) on individual MFCs for significant module pairs, simultaneously correcting for confounding variables, including age, gender, and education level. We then applied type-III analyses of covariance (ANCOVAs) to test the same effects (IMAG, LANG, and IMAG LANG) separately on the MFCs of each module pair, adjusted for age, gender, and education level. We reported any effects at p < 0.05 corrected for multiple comparisons, and at p < 0.05 uncorrected.

Results

Behavioral data

On average, the 307 participants reported spending 39% of the time on IMAG (SD = 21%, [min, max] = [0, 85%]) and 29% on LANG (SD = 19%, [min, max] = [0, 97%]; Fig. 1 and Table 1). The remaining 32% of the time was filled with a mixture of thoughts related to sensorial awareness, inner musical experience, or mental manipulation of numbers.

Functional connectivity of fMRI modules

The anatomical substrates of the five modules are presented in Fig. 2A. Among the 10 possible pairs of connected modules, 7 had correlation coefficients significantly different from 0 at the group level (p < 0.05, corrected for multiple comparisons; Fig. 2B). The average correlation coefficient and average MFC values are presented in Table S1.

Fig. 1. Two-dimensional frequency histogram of subjects with respect to the amount of time spent in visual mental imagery (IMAG) and inner language (LANG) during the 8-minute resting-state fMRI scan.
The effects of IMAG, LANG, and their interaction (IMAG LANG) on the MFCs of the seven significant pairs were investigated using a repeated-measures MANCOVA including age, educational level, and gender as confounding factors. We found a significant within-subject main effect of IMAG (F(6,295) = 3.93, p = 0.001), an interaction between IMAG and LANG (F(6,295) = 2.39, p = 0.029), and a significant between-subjects main effect of LANG (F(1,300) = 4.59, p = 0.033; Table S2).

Specific effects of IMAG and/or LANG on each of the seven pairs of modules, investigated using separate ANCOVAs, are shown in Fig. 3. Increased time spent in either IMAG or LANG significantly reduced functional connectivity between the “default-mode” (M1a) and “frontoparietotemporal” (M1b) modules (F(1,300) = 21, p<0.0001 and F(1,300) = 22, p<0.0001, respectively; Fig. 3). In addition, an IMAG LANG interaction was observed with this pair of modules (F(1,300) = 6.5, p = 0.01); the IMAG LANG interaction consisted of a
larger reduction in MFCs for participants reporting similar proportions of time spent in IMAG and LANG compared to those reporting predominant IMAG or LANG mental activity. The same effects were observed for MFCs between the intrinsic “frontal/supramarginal/subcortical” (M1c) and extrinsic “centrotemporal” (M2a) modules (IMAG: F(1,300) = 5.9, p = 0.02; LANG: F(1,300) = −3.9, p < 0.049; and IMAG LANG: F(1,300) = 4.3, p = 0.04; Fig. 3).

Increased time spent in IMAG, but not LANG, reduced the MFCs between the intrinsic “frontoparietotemporal” (M1b) and extrinsic “occipital” (M2b) modules (F(1,300) = 14.7, p = 0.0002). Notably this was the only effect occurring between modules with negative functional connectivity on average (r = −0.22 [mean]; Table S1). In contrast, MFCs between the “frontoparietotemporal” (M1b) and “frontal/supramarginal/subcortical” (M1c) modules were greater in participants reporting similar proportions of time spent in IMAG and LANG compared to MFCs in participants who reported having predominant IMAG or LANG activity (IMAG LANG interaction: F(1,300) = 4, p = 0.046). Finally, the MFCs between the “centrotemporal” (M2a) and “occipital” (M2b) modules increased with the proportion of time spent in IMAG (F(1,300) = 5.2, p = 0.02).

Discussion

This study was designed to explore the impact of self-reported mental content on functional connectivity in the brain during rest. A key finding was that increased time spent in either visual mental imagery or inner language was primarily associated with decreased functional connectivity within the intrinsic system, as well as between intrinsic and extrinsic systems. The opposite effect (i.e., increased functional connectivity with increased spontaneous mental activities) was scarce and occurred only between modules of the extrinsic system. We will discuss these results within the framework of functional segregation (i.e., decreased functional connectivity) and integration (i.e., increased functional connectivity) of modules according to their possible cognitive roles.

Functional segregation

The most significant negative effect was observed between two modules of the intrinsic system: the default-mode (M1a) and frontoparietotemporal (M1b) modules. Reduced modular functional connectivity was found for each type of mental activity, with the greatest negative effect when both types of activities occurred at similar proportions. This effect reflects functional segregation in the intrinsic system between the regions associated with the generation of mind wandering (via M1a) (Buckner et al., 2008) and those engaged in the manipulation and maintenance of spontaneous thoughts (via M1b) (Wager and Smith, 2003). We suggest that this segregation is characteristic of thinking during rest; it provides a fundamental distinction between goal-directed cognition and daydreaming. In goal-directed cognition, the effectiveness of goal reaching is based on coordination between networks specific to the task performed and the networks in charge of maintenance and manipulation of information. In daydreaming, the spontaneous sequence of thoughts during rest is not constrained by any logic, causality, or even a rigorous temporal organization, which may be the cause of the negative effects we report. This lack of organization is reflected by the decreased functional connectivity between the default-mode module (M1a) and frontoparietotemporal module (M1b), which act in the generation of spontaneous thoughts and maintenance and manipulation, respectively.

Negative effects were also observed between the frontal/supramarginal/subcortical (M1c) module of the intrinsic system and the sensory/motor/attentional (M2a) module of the extrinsic system. Segregation between internally and externally oriented modules is expected when one’s mind is turned towards internal goals (Menon and Uddin, 2010). We suggest that this functional segregation is related to the reduced engagement of this unimodal and associative module, which includes the dorsal attentional network (Corbetta and Shulman, 2002; Petit et al., 2009), during mind wandering under the control of the M1c module.

A specific effect of visual mental imagery was found between the visual (via M2b) and parietofrontal (via M1b) areas. Functional segregation by thought content appears to be strengthened between modules that are negatively correlated (Fig. 2 and Table S1). This observation is supported by what occurs during actual dreaming: the visual and prefrontal cortices have been described as having dissociative activity (Braun et al., 1998). A negative temporal correlation between the visual cortex and parietofrontal network underlies the difference between goal-directed imagery and spontaneous mental imagery occurring during rest; the former involves maintenance and transformation of information, requiring cooperation between the fronto-parietal cortex and visual areas (Ganis et al., 2004; Mechelli et al., 2004; Mellet et al., 1998), whereas the latter has been found to have no positive functional relationship between the visual areas and high order associative cortex.

Functional integration

An interaction was detected between the module including the frontal cortex, supramarginal gyri, and subcortical areas (M1c) and the frontoparietotemporal (M1b) module within the intrinsic system. These modules exhibited increased functional connectivity when subjects reported similar IMAG and LANG proportions rather than predominant IMAG or LANG. Christoff et al. (2009) suggested that the executive brain regions, most notably the dorsal anterior cingulate cortex (in M1c) and dorsolateral frontal cortex (in M1b), are recruited to contribute to mind wandering. Previous behavioral studies have suggested that mind wandering depends on central executive resources (Smallwood and Schooler, 2006; Teasdale et al., 1995). In this context, we propose that the strengthened functional connectivity between modules covering executive regions (M1b and M1c) underlies their functional involvement in the mixing of image- and language-based free-association thoughts.

Functional connectivity between the two modules of the extrinsic system increased with increasing visual mental imagery. Previous studies have proposed that brain areas that are not task relevant enter an “idling state” characterized by neural synchronization (Pfurtscheller et al., 1996). These areas, which are part of the extrinsic system, have been described as being engaged in goal-directed processing (Golland et al., 2008; Vanhaudenhuyse et al., 2010). In this context, the present findings suggest that unimodal associative areas increase their synchronization to implement a common “idling” state.

Overall picture

Our results provide evidence that both dominant mental activities, visual mental imagery and inner language (Delamillieure et al., 2010; Mazoyer et al., 2001), are associated with a strengthening of the temporal anti-correlation between the intrinsic and extrinsic systems. Therefore, the findings support previous observations that the brain is functionally organized into two anti-correlated large-scale networks (Fox et al., 2005; Golland et al., 2008). These results are consistent with the hypothesis that the resting state favors a focus on internally oriented thoughts (Teasdale et al., 1995). Strikingly, the negative functional connectivity between the default-mode network (via M1a) and dorsal attentional network (via M2a) (Fox et al., 2005; Fransson, 2005) was not modified by the mental content. We conclude that these temporal correlations, which are already at a very negative level (Table S1), could not be further anti-correlated.

On the other hand, we demonstrated that the intrinsic system is supported by a complex interplay between three modules. Most
intriguing is the observation that the frontoparietotemporal module (M1b), known to subserve manipulation and maintenance of thoughts, concentrates a majority of the significant modulations in synchronization. Although temporal correlation is not equivalent to activation, the pattern of significant modulations we observed is compatible with a central role for this module during the resting state. When considered in light of previously published literature suggesting increased engagement of the default-mode regions during mind wandering (Mason et al., 2007; McKiernan et al., 2006), our observation of decreased functional connectivity of default-mode regions (M1a) for both visual mental imagery and inner language thoughts seems counterintuitive. This decrease may be a functional signature of spontaneous cognition; it could be the neural support of the unconstrained and unsupervised nature of such thoughts driven by free association.

Taken together, these results demonstrate that, although spontaneous thoughts shape the regional synchronization of low-frequency oscillation patterns, they also account for only a small fraction of the variance. This observation might be related to the intrinsic limitations of the retrospective questionnaire, which cannot capture unassessed thinking (Hurlburt and Akhter, 2008). Indeed, these types of questionnaires depend upon the accuracy of retrieval and, more generally, upon the awareness of the subject (Christoff et al., 2009). Similarly, the effect of time spent in somatosensory awareness, which was previously shown to be reported often but at a low percentage by participants (Delamilliere et al., 2010), might not have been seen with the proposed analysis, as we relied on the variability of behavioral measurements to make inferences. Recent investigations have identified effects of some factors that participate in the variance of low-frequency oscillation at rest and are unrelated to inner experience, such as genes (Fornito et al., 2011; Glahn et al., 2010), development (Dosenbach et al., 2010; Fair et al., 2007), aging (Achar and Bullmore, 2007; Allen et al., 2011), and psychiatric disorders (Jafari et al., 2008). The resting state patterns of temporal coherence have been proposed to be devoted to the ongoing coordinated activity of all brain systems (Raichle, 2010), possibly in a Hebbian-like process. Future research may try to study the interaction between such activity and spontaneous thought-related activity to get an overall picture of low-frequency oscillation phenomena. Finally, setting up a comparison between mind wandering and goal-directed activity in the same individuals could be a next step.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2011.11.059.

References


