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A Brief History of the Resting State: the Washington University Perspective

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Abstract

We present a history of the concepts and developments that have led us to focus on the resting state as an object of study. We then discuss resting state research performed in our laboratory since 2005 with an emphasis on papers of particular interest.

Introduction

It has been appreciated for at least two millennia that the brains of humans exhibit ongoing activity regardless of the presence or absence of any observable behaviors. As noted by Seneca in ~60 A.D., “*The fact that the body is lying down is no reason for supposing that the mind is at peace. Rest is... far from restful*” (Seneca, 1969). However, scientific investigation of the brain’s “resting state” presents conceptual as well as methodological challenges whereas studying the brain’s responses to controlled stimuli, that is, the experimental paradigm that has dominated systems neuroscience throughout the latter half of the 20th century, is comparatively straightforward. An expanded view of the tension between task-based and resting-state modes of investigation has been outlined in a recent review (Raichle, 2009). Below we present a brief account of scientific milestones that have shaped our view of the resting state. We then briefly review the history of resting state fMRI studies performed our laboratory.

“Resting state” defined

Given the apparently contradictory characterization of “rest” (see above) it is prudent to begin with a definition. In the context of experimentation, “rest” is an operational definition referring to a constant condition without imposed stimuli or other behaviorally salient events. The eyes may be closed or open, with or without visual fixation. The operational definition of “rest” may be generalized to encompass engagement in a controlled task as long as all imposed temporal structure is randomly phased with respect to the fMRI acquisition e.g., (Fransson, 2006). The objective of resting state experiments is to capture the statistical properties of endogenously generated (synonyms: spontaneous; intrinsic) neural activity. In contrast, the objective of event-related studies is to measure evoked or induced responses.

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During quiet wakefulness, humans experience stimulus independent thoughts (Antrobus, 1968; Christoff et al., 2009; Mason et al., 2007), the cognitive content of which is not easily related to objectively measurable fMRI responses (for recent examinations of this issue see (Gruberger et al., 2011; Hasenkamp et al., 2011; Stawarczyk et al., 2011)). Hence, the resting state is uncontrolled according to the usual conventions that apply in cognitive neuroimaging. This circumstance has provoked strongly worded objections to resting state studies altogether (Morcom and Fletcher, 2007). But resting state studies are motivated in large part by questions of neurobiology, not cognitive theory (see below).

Moreover, although resting state fMRI as a technique does not support conventional measurement of event related responses, resting state studies during the past few years have shown that the statistical properties of endogenous activity are modulated by the state of the eyes (Bianciardi et al., 2009; McAvoy et al., 2008), by concurrent performance of semantic (Fransson, 2006) and motor tasks (Sun et al., 2007) and by concurrent sensory stimulation (Hampson et al., 2004). Similar modulations have also been observed immediately following task performance (Albert et al., 2009; Stevens et al., 2010; Waites et al., 2005). These effects provide clues regarding the physiological significance of resting state activity.

Before proceeding, we note that unconstrained cognition alone does not account for the greatest part of intrinsic activity although it undoubtedly contributes a small increment. The principal reasons for this assertion may be stated as follows: (i) Imposed tasks evoke responses that are modest in magnitude in comparison to intrinsic activity (Raichle and Mintun, 2006). This is why averaging is required to extract meaningful responses from the ongoing background. There is no reason to suppose that unconstrained thoughts are more energy demanding than constrained ones. (ii) Resting state activity persists, albeit in modified form, during slow wave sleep (Samann et al., 2011) and even during surgical anesthesia (Vincent et al., 2007), states in which cognition generally is assumed to be absent or at least very attenuated. Hence, something other than unconstrained cognition must be posited to account for most intrinsic activity (see (Raichle, 2009, 2010) for additional discussion of this point).¹

Some history

The first scientist to explicitly address the significance of patterned nervous activity may have been Thomas Henry Huxley, in his book on the crayfish (Huxley, T, 1884). Huxley wrote, *“If the nervous system were a mere bundle of nerve fibers extending between sensory organs and muscles, every muscular contraction would require the stimulation of that special point of the surface on which the appropriate sensory nerve ended. The contraction of several muscles at the same time, that is, the combination of movements towards one end, would be possible only if the appropriate nerves would be stimulated in the proper order, and every movement would be the direct result of external changes. The organism would be like a piano, which may be made to give out the most complicated harmonies, but is dependent on the depression of a separate key for every note that is sounded. But it is obvious that the crayfish needs no such separate impulses for the performance of highly complicated actions. ... To carry the analogy of the musical instrument further, striking a*

¹It is not self evident that unconstrained cognition does not, in large part, account for ongoing neural activity. In 2006, we submitted a manuscript on the default mode network (DMN) and the dorsal attention network (DAN; Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. *Nature reviews. Neuroscience* 3, 201–215.), showing that the topography of resting state correlation maps closely matches responses obtained by conventional task-based fMRI. Although this work was ultimately published (Vincent, J.L., Snyder, A.Z., Fox, M.D., Shannon, B.J., Andrews, J.R., Raichle, M.E., Buckner, R.L., 2006. Coherent spontaneous activity identifies a hippocampal-parietal memory network. *Journal of neurophysiology* 96, 3517–3531.), a reviewer of the submitted manuscript wrote, *“The absence of behavioral events does not necessarily mean that there is an absence of cognitive events. Perhaps fluctuations in voluntary attention to sensory stimuli (which are always present even in the absence of experimental presentation) and fluctuations in voluntary episodic recollection are driving the resting state correlations.”*

single key gives rise, not to a single note, but to a more or less elaborate tune; as if the hammer struck not a single string, but pressed down the stop of a musical box." Huxley emphasized the extent to which the crayfish exhibits highly organized behaviors in response to the simplest stimuli. This principle applies as well to more advanced animals including humans: Almost everything we do is automatic (Hikosaka and Isoda, 2010; Saling and Phillips, 2007)². But, the crayfish has an extremely limited capacity to modify its behavioral repertoire on the basis of experience, that is, to acquire automatized responses. Hence, the crayfish does not require abundant ongoing neural activity unrelated to emergent behavior.

In 1933, George Bishop (Bishop, 1933) observed cyclic changes of excitability in the visual cortex of the rabbit during stimulation of the optic nerve. Bishop commented, *"In general, it is not necessary to infer that each individual impulse traveling up a fiber from the retina arrives as a unit impulse in the cortex, and registers there as such. Rather, we would look upon the cortex as being in constant activity, the physiological activity of the whole network of neurons bearing some direct relationship to the 'present state' of the animal's complex behavior which is sometimes referred to as his 'mental state'".* Thus, Bishop clearly understood that the brain's response to stimuli is modulated by fluctuating endogenous activity. More recent, fMRI-based examples of this principle include the demonstration that percepts as well as actions are modulated by ongoing activity (for review see (Sadaghiani et al., 2010)). The same perspective underlies studying the cognitive significance of trial-to-trial variability in evoked responses (Arieli et al., 1996; Debener et al., 2007). These experiments are grounded in the view, articulated in the early part of the 20th century by the physiologist T. Graham Brown (Brown, 1914), that the brain's operations are mainly intrinsic, involving acquisition and maintenance of information for interpreting, responding to and even predicting environmental demands. In 1996, Lawrence R. Pinneo forcefully argued that ongoing neural activity ("noise") is essential to brain function (Pinneo, 1966). Pinneo related tonic neural activity to arousal and suggested that this activity is what enables the brain to efficiently respond to environmental events. These ideas antedate by at least 25 years similar notions that today are discussed under the heading of stochastic resonance (McDonnell and Abbott, 2009).

In 1929, Hans Berger reported the first human EEG recordings (Berger, 1929) (for an English translation see (Gloor, 1969)). Berger understood that the EEG was related to mental activity and posed the question, *"Is it possible to demonstrate the influence of intellectual work upon the human electroencephalogram, insofar as it has been reported here?"* He concluded: *"Of course, one should not at first entertain too high hopes with regard to this, because mental work, as I explained elsewhere, adds only a small increment to the cortical work which is going on continuously and not only in the waking state."* Recent studies have shown that, indeed, it is possible to detect volitionally induced changes in the statistical properties of the EEG and, using this technology, provide paralyzed humans with some control over their environment via robotic devices (Birbaumer and Cohen, 2007). However, the computational significance of the EEG as a whole remains largely unknown.

The advent of electronic computers following the second world war enabled the development of averaged evoked response potential (ERP) recording, introduced in 1954 by G. D. Dawson (Dawson, 1954). Heretofore, the EEG had remained much as developed by Berger, that is, polygraphic tracings on paper. Response averaging enabled researchers to extract reproducible waveforms from the ongoing EEG and relate these responses to controlled stimuli. This basic paradigm was carried forward as new techniques for acquiring

²Cognitive errors arising out of automatic behaviors often are comical (Reason, J., Mycielska, K., 1982. *Absent Minded?* Prentice-Hall, Englewood Cliffs, NJ.) but also are the cause of serious man-made disasters (Reason, J., 1990. *Human Error*. Cambridge University Press.)

physiological data became available, e.g., single unit recording, optical imaging and ultimately, fMRI. Until recently, the preponderance of neuroscience research has been conducted by averaging away anything not phase synchronous with events of interest.

Metabolic investigations of the resting state also date to the years following the second world war. In 1948, Seymour Kety and Carl Schmidt introduced the first quantitative measurements of human, whole-brain blood flow and metabolism (Kety and Schmidt, 1948). Kety, Sokoloff and their colleagues noted that, while the human brain is only 2% of the body weight, it accounts for 20% of the body's energy consumption, ten times the amount expected on a per weight basis. These measurements were, of course, made in the resting state. In 1955, the same group had normal subjects perform a difficult mental arithmetic task while whole-brain blood flow and oxygen consumption were measured. When these measurements were compared with the resting state in the same subjects, no change in either whole-brain blood flow or oxygen consumption (a measure of energy expenditure) was observed (Sokoloff et al., 1955). These observations were extended to regional measurements with PET in the 1980s ((Fox et al., 1988); for reviews see (Raichle, 2010; Raichle and Mintun, 2006)) in which it was shown that locally induced changes in blood flow were accompanied by proportionate increase in glucose consumption but not oxygen utilization. These results made understandable the earlier observation of the absence of an energy cost for mental 'work' (Sokoloff et al., 1955). The local changes were too small to have been detected by methods designed to measure the energy consumption of the brain as a whole. As so often happens in science, these results were anticipated in a remarkably prescient analysis by the late Otto Creutzfeldt (Creutzfeldt, 1974).

An important additional perspective on the energy cost of the resting state emerged with the analysis of glutamate cycling by David Attwell and Simon Laughlin (Attwell and Laughlin, 2001) and others (e.g., see (Ames, 2000; Lennie, 2003)). These studies showed that transmitter cycling, a hallmark of brain functional activity, accounts for the overwhelming majority of the brain's enormous metabolic cost. Studies employing MR spectroscopy and stable isotopes of glucose (Sibson et al., 1997; Sibson et al., 1998) came to the same conclusion. Thoughtfully considered, these data present a challenge to those wishing to study brain function when it is realized that most of the brain's activity is intrinsic.

Thus, the resting state is not truly a resting state at all. But, having acknowledged this, it has not until recently been entirely clear how to undertake a study of intrinsic activity. It is for this reason that the vast majority of studies of the brain of humans and laboratory animals consisted of provoking a change in brain activity and monitoring the features of that change with microelectrodes, optical techniques and imaging devices such as MRI and PET. In fact, the idea that one would include a resting state in studies of the human brain was considered unacceptable by cognitive neuroscientists because it completely lacked the features of an adequately designed 'control state'. Despite this concern some did, indeed, include a resting state in their imaging studies and we were, unashamedly, among them! The results of doing so were surprising and most interesting. These appeared as activity decreases from a resting state during the performance of goal-directed tasks.

The first formal characterization of task-induced activity decreases from a resting state derived from a large meta-analysis of published PET data from our group (Shulman et al., 1997). This study generated iconic images of a constellation of brain regions now generally referred to as the default mode network or DMN, after our later paper on a *default mode of brain function* (Raichle et al., 2001). The unique identity of the DMN was amply confirmed in later meta-analyses by Jeffery Binder and colleagues (Binder et al., 1999) and by Bernard Mazoyer and colleagues (Mazoyer et al., 2001). It is currently widely accepted that a specific set of brain areas decreases activity during performance of a remarkably wide range

of tasks as compared to a control condition such as visual fixation (see also article by Jeff Binder in this volume).

The observation of task-induced activity decreases exhibiting a stereotypical topography was surprising because the involved areas had not previously been recognized as a functional system in the same sense as, say, the motor or visual systems. Compelling evidence of a DMN equivalent has since been demonstrated in the monkey (Mantini et al., 2011) and suggestive evidence has been found in the cat (Popa et al., 2009) and mouse (White et al., 2011). However, at the time, many argued, informally, that these activity decreases were simply activations induced by a poorly constrained resting state. To determine whether or not task-induced activity decreases were simply 'activations' in the absence of an imposed task we employed quantitative PET measurements of regional brain blood flow and oxygen consumption to define a physiologic baseline. The details of this work have been recounted on several occasions (Gusnard and Raichle, 2001; Raichle et al., 2001; Raichle and Mintun, 2006; Raichle and Snyder, 2007) and will not be repeated here. The PET results showed that activity within the DMN did not represent conventional activations in the resting state but, rather, a new view of the organization of the brain's intrinsic activity. The operations represented in the DMN were attributed to 'a default mode of brain function' because they are most active when subjects are not engaged in goal-directed task performance (Raichle et al., 2001). It is important to note that the DMN is not unique in exhibiting both high levels of baseline metabolism and organized functional activity in the resting state. These are properties of all cortical functional systems and their subcortical connections.

Precursors of resting state fMRI

Spontaneous fluctuations in regional oxygen availability have been actively investigated since the 1950s (for an excellent review see (Hudetz et al., 1992)). In retrospect, it is clear that these fluctuations represent the same physiology as spontaneous fluctuations of the BOLD signal (Ogawa et al., 1990; Pauling and Coryell, 1936) but the connection to fMRI was not established until much later (see also articles by Keith Thulborn, Peter Fox and Seiji Ogawa in this volume). In fact, these early physiological observations preceded all imaging by almost two decades! Oxygen availability was measured with oxygen sensitive electrodes placed on the cortex of experimental animals and patients undergoing evaluation for epilepsy surgery. Routinely observed in these studies were slow (<0.05 Hz) variations in oxygen availability along with stimulus/task induced increases (Cooper and Crow, 1975). Much speculation surrounded the origin and significance of these oxygen waves (for an interesting discussion see (Purvis, 1978)) concerning how they might relate to ongoing metabolism and whether might reflect opening and closing of capillaries. The metabolism hypothesis received support when it was demonstrated that oxygen waves reflected regional fluctuations in the brain's redox state that, remarkably, were synchronous in homologous regions of both hemispheres (Vern et al., 1997, 1998). The issue of capillary opening and closing fell by the wayside, in part, because of the demonstration of homologous synchrony. Finally, these spontaneous waves of blood flow and oxygen availability were related to patterns of electrical activity in experimental animals (Golanov et al., 1994), a subject of immense current interest (e.g., (He et al., 2007b; Lu et al., 2007)). Bharat Biswal and his colleague, Antal Hudetz, were well aware of this legacy (Biswal and Hudetz, 1996) when they performed their seminal experiment on resting state fMRI correlations (Biswal et al., 1995) (see also article by Bharat Biswal in this volume).

Resting state fMRI

It had been known since the advent of fMRI that the BOLD signal exhibits slow (nominally, < 0.1 Hz) spontaneous fluctuations although this phenomenon was initially regarded as noise (Purdon and Weisskoff, 1998). However, that these fluctuations are of neural origin was not established until Bharat Biswal and colleagues demonstrated that resting state BOLD signals are temporally correlated within the somatomotor system (Biswal et al., 1995). The neuroscience community, with few exceptions, was remarkably slow to take note of this important result. For an excellent account of this history see (Lowe, 2010). Much emphasis was placed on non-neuronal, that is, artifactual sources of correlated fMRI signals, e.g., head motion (Friston et al., 1996), cardiac pulsations (Glover and Lee, 1995) and variable arterial pCO₂ (Wise et al., 2004). To be sure, the importance of recognizing the existence of these artifacts and of developing techniques to minimize their impact (e.g., (Deckers et al., 2006; Jo et al., 2010; Jones et al., 2008)) cannot be overstated. However, during the first few years following the demonstration that resting-state BOLD correlations recapitulate the topography of task-evoked responses, skepticism regarding the biological significance of this effect outweighed acceptance. Most resting state fMRI studies used very short TRs to reduce the impact of physiological pulsations (e.g., (Lowe et al., 1998)), an unavoidable consequence of which was limited coverage. Another characteristic of this early period was the tendency to attribute coherent physiological signals to the vasculature rather than the brain (Mitra et al., 1997).

The significance of resting state BOLD signal correlations was brought forcefully to our attention when Michael Greicius and colleagues generated an image of the DMN using a seed region of interest in the posterior cingulate cortex (Greicius et al., 2003). Similar patterns of resting state coherence have now been documented in most cortical systems in the human brain (Fox and Raichle, 2007; Thomas Yeo et al., 2011) as well as their subcortical connections (Barnes et al., 2010; Buckner et al., 2011; Di Martino et al., 2008) (for reviews see (Cole et al., 2010; Fox and Raichle, 2007; Lowe, 2010; Uddin et al., 2011; Wig et al., 2011)).

Survey of resting state studies at the Washington University School of Medicine Neuroimaging Laboratories (NIL)

Seed-based correlation mapping is but one of several techniques used at the NIL to investigate the resting state. A comprehensive listing of all NIL papers on resting state activity published since 2005 is provided in Supplementary Information. Each paper is assigned to one or more related headings: *Neuroscience*; *Analysis methodology*; *Mapping*; *Pathophysiology*; *Development and aging*; *State-dependent functional connectivity*; *Inter-individual differences*; *Review*. These headings are briefly discussed below with an emphasis on selected contributions from the NIL.

Neuroscience

The “neuroscience” heading refers to investigations bearing on the fundamental nature of resting state activity. It is generally assumed, for good reasons, that intrinsic fluctuations of the BOLD signal reflect electrophysiological activity. Logothetis and colleagues have amply demonstrated this principle in the context of task performance (Goense and Logothetis, 2008; Logothetis et al., 2001) (see also article by Nikos Logothetis in this volume). Extension of this result to the resting state is attributable to (Shmuel and Leopold, 2008). Our contribution to this question includes a study showing a correspondence, in individuals, between the topography of BOLD resting state networks and the correlation structure of electrocorticographically (ECoG) recorded resting state slow cortical potentials (He et al.,

2008). In related work, we and colleagues at the University of Chieti demonstrated a correspondence between fMRI RSNs and magnetoencephalographically (MEG) recorded intrinsic activity (de Pasquale et al., 2010). Similar results have since been obtained by others (Brookes et al., 2011) (see also article by Helmut Laufs in this volume). But, accepting that spontaneous BOLD signal fluctuations do reflect electrophysiology, this leaves unsolved the fundamental problem of defining what intrinsic activity contributes to brain function.

One set of results that informs this question derives from our demonstration that resting state networks, including the DMN, are present in anesthetized monkeys (Vincent et al., 2007). The implications of this finding extend far beyond establishing monkey-human homologies: (i) The persistence of RSNs in the anesthetized state represents one of the key observations that render untenable the notion that unconstrained cognition accounts for most resting state activity (see also above). Several laboratories have reported similar demonstrations in sedated humans (e.g., (Muirheartaigh et al., 2010; Peltier et al., 2005)). Anesthesia as an experimental intervention is closely related to the topic of state-dependent resting state activity, which is covered under a separate heading (see below) (ii) The existence of a DMN in subhuman primates raises interesting questions concerning the cognitive role of this functional system, which, in humans, is thought to include moral reasoning, model building and prospection (Buckner et al., 2008; Schacter et al., 2007) (see also article by Randy Buckner in this volume). The problem is that these labels suggest intellectual capacities found only in humans whereas the DMN is certainly present in monkeys (Mantini et al., 2011) and may be present as well in the mouse (White et al., 2011). If, as appears increasingly likely, all mammals have a DMN, currently prevailing theories concerning the cognitive operations represented in the DMN will have to be revised. (iii) Our report on RSNs in anesthetized monkeys (Vincent et al., 2007) also includes one of the earliest elaborations on the point that the correspondence between functional and anatomical (axonal) connectivity is not one to one (for a recent paper on this topic see (Deco et al., 2011)). Other work bearing on this question includes our demonstration that inter-hemispheric functional connectivity is effectively obliterated in the acute period (days) after complete section of the corpus callosum (Johnston et al., 2008). This result seems to reinforce the notion that functional connectivity is closely tied to anatomic connectivity. But other laboratories have shown that interhemispheric functional connectivity may be present decades after total corpus callosotomy (Uddin et al., 2008), which reinforces the point that RSNs substantially reorganize after injury. We have seen suggestions of such reorganization in the context of pre-surgical RSN mapping in patients with brain tumors (Zhang et al., 2009). This reorganization itself represents another clue regarding the physiological functions of resting state activity.

Analysis methodology

Two complementary analysis strategies, seed based correlation mapping and spatial ICA (sICA; see also article by Christian Beckmann in this volume) (Beckmann et al., 2005), currently dominate the field of resting state fMRI. Seed based correlation mapping provides a natural means of investigating the functional connectivity of *a priori* targeted regions of interest but requires extensive preprocessing to minimize the influence of non-neuronal sources of variance. In contrast, ICA provides a direct means of separating artifact from neural signals but is less suited to investigating targeted regions of interest.³ Both strategies yield highly reproducible results (Damoiseaux et al., 2006; Shehzad et al., 2009). However,

³Mugs and T-shirts are available to proponents of ICA and seed-based correlation mapping at <<http://www.cafepress.com/neurobureau/7193595>>. The ICA logo reads, "ICA is for people who don't know what they want." The alternative logo is "Seed-based Correlation Analysis. *Because you have the balls to hypothesize.*" "Balls" refers to the practice of centering spherical regions interest on *a priori* defined coordinates.

the topography of certain resting state networks (RSNs) derived by the two methods systematically differ. Specifically, certain RSNs typically obtained by sICA ('C' and 'D' in (Damoiseaux et al., 2006)) are lateralized whereas seed-based correlation mapping generally yields highly symmetric maps (Vincent et al., 2006). It is therefore noteworthy that the topography of the DMN appears more or less the same regardless of which method is used; this invariance speaks to the highly robust character of the DMN.

Soon after the NIMH became committed to resting state fMRI, several of us worked on improving technical aspects of seed-based correlation mapping. Global signal regression (GSR), that is, using the timeseries averaged over the whole brain as a nuisance regressor during preprocessing, was implemented as a strategy for reducing the influence of spurious variance, e.g., artifact attributable to fluctuating pCO₂ (Birn et al., 2006; Chang and Glover, 2009) (see also article by Rasmus Birn in this volume). GSR was observed to dramatically improve the spatial specificity of correlation maps (Fox et al., 2009; Macey et al., 2004). One of the most striking features of correlation maps obtained using GSR is anti-correlation between the DMN and a set of regions that we named the "task positive network" (TPN) (Fox et al., 2005). Today, we identify the TPN as encompassing both the dorsal attention network (DAN) (Corbetta and Shulman, 2002) and areas associated with cognitive control (Dosenbach et al., 2007; Seeley et al., 2007; Vincent et al., 2008). Negatively correlated DMN-TPN activity in the resting state recapitulates the opposed DMN-TPN dynamics induced by task performance. We are persuaded that this recapitulation reflects a fundamental principle of brain organization. Most recently, the DMN vs. TPN distinction was found to correspond to regional differences in metabolic parameters (Vaishnavi et al., 2010), which, in turn, closely correspond to regional differences in susceptibility to the effects of Alzheimer's disease (Bero et al., 2011; Vlassenko et al., 2010).

GSR has turned out to be hugely contentious (Anderson et al., 2011; Murphy et al., 2009). This is partly our fault, since we did not, in 2005 (Fox et al., 2005) or even in 2009 (Fox et al., 2009), clearly articulate that the BOLD signal everywhere represents a superposition of spatio-temporal components, some of which are neural and some of which are artifact; this superposition is implicit in ICA. Correlation mapping following GSR is algebraically similar to partial correlation mapping of order one controlling for widely shared variance. GSR removes widely shared variance, thereby uncovering more specific relations. But, a consequence of GSR is that, in all subsequently computed correlation maps, the mean value is algebraically constrained to be approximately zero. (This result is exactly correct in application to beta maps (Fox et al., 2009)). Hence, GSR may be viewed as artificially generating negative correlations. However, absent GSR, all correlations would be positively biased by spatially non-specific variance, some unknown fraction of which undoubtedly is artifact. Recent evidence suggests that the global signal includes a substantial component of neural origin (Scholvinck et al., 2010). Therefore, the advantages of GSR (improved spatial specificity) may come at the cost of removing from the analysis global components of truly neural origin.

It has been our practice, since 2005, to prepare resting state data for correlation mapping using several procedures in addition to conventional fMRI preprocessing (e.g., head motion correction, see (Shulman et al., 2009) for a complete account). Spatial smoothing (6 mm FWHM in each direction) and temporal smoothing (low pass, retaining frequencies below 0.1 Hz) are applied early in the pipeline, that is, before nuisance regression. The logic underlying the 0.1 Hz figure is that all available evidence indicates that BOLD modulations of neuronal origin are essentially absent above this frequency (Hathout et al., 1999), whereas artifacts of various origin, including aliased cardio-pulmonary pulsations, are not. We originally (Fox et al., 2005) excluded from correlation analyses frequencies below 0.009 Hz simply because that was standard practice in GLM-based analyses of task-based fMRI.

However, it appears that intrinsic neuronal activity, at least as reflected in the BOLD signal, is “1/f-like” (He et al., 2010), which means that no advantage accrues from ignoring the lowest measurable frequencies; we no longer do so. Following spatio-temporal filtering, artifact reduction is accomplished by regression of multiple waveforms, in addition to the global signal: six rigid body head motion parameters (derived by retrospective motion correction) and the timeseries extracted from one white matter region and one cerebrospinal fluid region (Fox et al., 2005). Several laboratories have developed variants of this strategy avoiding GSR and relying, instead, on nuisance regressors derived from multiple regions of high noise-to-signal ratio (Chai et al., 2012; Jo et al., 2010; Weissenbacher et al., 2009). It is likely that we will employ similar multiple nuisance regressor techniques in the future. Finally, volume censoring (“scrubbing”; (Power et al.; Smyser et al., 2010)) has been standard practice in our laboratory during the past year or so.

NIL contributions to seed-based correlation mapping technique include our demonstration that partial correlation (order 4 but omitting GSR) may be used to map functional connectivity between thalamic voxels and broad parcels of the cerebral cortex (Zhang et al., 2008). This technique maps thalamo-cortical functional connectivity with specificity comparable to that obtained by diffusion tensor tractography (Zhang et al., 2010). A more thorough investigation of the relations between anatomic and functional connectivity will be undertaken in the context of the Human Connectome Project (HCP; <<http://humanconnectome.org>>; see also article by David van Essen and Kamil Ugurbil in this volume), in which the NIL is a participant. One of the objectives of the HCP is to compute parcellations of the cerebral cortex, at both the individual and group levels, on the basis of resting-state fMRI. Novel methodologies for determining the boundaries between RSNs developed at the NIL (Cohen et al., 2008) will be applied to this end. The NIL also has advanced the use of graph theoretic techniques (for reviews see (Bullmore and Sporns, 2009) and article by Olaf Sporns in this volume) to delineate RSNs (e.g., (Barnes et al., 2010; Power et al.)) and to track the development of RSNs as a function of age (Power et al., 2010). Seed-based correlation (including GSR) is at the front end of all graph-theoretic analyses so far performed at the NIL. Most recently, we have shown that head motion, even that of relatively modest amplitude, gives rise to artifact that biases measured correlations positively at short range but negatively at longer range; and, that this artifact is not eliminated by regression of motion parameters (Power et al.). Frame censoring (“scrubbing”) can be used to reduce the impact of this artifact in the context of correlation mapping.

Mapping

The immediate objective of mapping experiments is to delineate the topography of RSNs. The underlying objective is to study the topographic correspondences between task-evoked responses and RSNs (e.g., (Dosenbach et al., 2007; Fox et al., 2006; Fox et al., 2005; Lewis et al., 2009; Nelson et al., 2010; Sestieri et al., 2011; Shannon et al., 2011; Vincent et al., 2008; Vincent et al., 2006)). Such correspondences offer a means of assigning functionality to observed RSNs, and, conversely, of reshaping theoretical models of cognition (see article by Russ Poldrack in this volume). Thus, for example, social cognition and episodic recall are both represented in the same RSN (the DMN). This association suggests a biological link between two seemingly disparate functions. We hasten to add that we do not here claim to understand this link, only that its existence is implied by evidence derived from resting state mapping studies. On a more practical note, we are exploring the utility of resting state RSN mapping to delineate eloquent cortex prior to neurosurgical procedures (Zhang et al., 2009). Several groups, using either sICA (Doucet et al., 2011) or seed-based correlation mapping (including GSR; (Thomas Yeo et al., 2011)) have advanced RSN mapping to the point that

accounts for nearly the entire cerebral cortex. The NIL's contribution to this effort uses both correlation mapping and graph-theoretic techniques (Power et al.).

Pathophysiology

Many neurological and psychiatric entities give rise to resting state functional connectivity changes (Fox and Greicius, 2010; Zhang and Raichle, 2010). Original NIL contributions to this field have concentrated on neglect and motor disability consequent to stroke (Carter et al., 2010; Carter et al., 2011; He et al., 2007b), Alzheimer's disease (Sheline et al., 2010a; Sheline et al., 2010c), depression (Sheline et al., 2010b), traumatic brain injury (MacDonald et al., 2008), prematurity at birth (Smyser et al., 2010) and Tourette's syndrome (Church et al., 2009).

Pizoli and colleagues (Pizoli et al., 2011) very recently reported dramatic *improvement* in functional connectivity architecture following anterior 2/3 corpus callosotomy in a child with epileptic encephalopathy (Lennox-Gastaut syndrome). The most notable feature of this case was the observation of pre-treatment resting state abnormalities attributable to nearly complete suppression of spontaneous BOLD fluctuations, which abnormality remitted after treatment in concert with a dramatic improvement in the patient's clinical status and EEG. This paper represents, as far as we are aware, the first report of direct evidence linking spontaneous resting state activity with the development and maintenance of normal brain function.

Development and aging

NIL investigators have examined the development of RSNs in newborn (premature and term) infants (Smyser et al., 2010) and children (Fair et al., 2010; Fair et al., 2008; Fair et al., 2009; Fair et al., 2007). One theme that emerges from these studies in aggregate is that long-range functional connectivity between posterior and anterior nodes of the DMN retrogresses in old age (Andrews-Hanna et al., 2007) suggesting reversal of the sequence of development during early childhood.

State-dependent functional connectivity

NIL investigators have studied the effects of eye closure in quietly resting, awake humans (McAvoy et al., 2008), early sleep in normal humans (Larson-Prior et al., 2009) and variable depth anesthesia in monkeys (Vincent et al., 2007). Maurizio Corbetta and colleagues at the University of Chieti, Italy, have shown that intensive perceptual training (several hours per day for several days) alters functional connectivity within task-relevant parts of the brain (Lewis et al., 2009). This result is consistent with a Hebbian view of experience-dependent synaptic enhancement.

Inter-individual differences

Several laboratories have demonstrated a correspondence between individual cognitive performance measures and resting state functional connectivity (e.g., (Song et al., 2008)). At the NIL, Shannon and colleagues studied a cohort of 107 incarcerated juvenile offenders and observed that impulsivity scores correlated with functional connectivity bilaterally in dorsal premotor cortex (PMdr) (Shannon et al., 2011). In greater detail, resting state BOLD fluctuations in PMdr correlated with the DMN in impulsive individuals; conversely, fluctuations in PMdr correlated with functional systems associated with cognitive control in non-impulsive individuals. Moreover, in a separate cohort of normally developing teenagers and young adults, the impulsivity-associated pattern was found to be a correlate of youth. Thus, impulsivity in juvenile offenders may be a consequence of delayed brain maturation rather than an immutable trait. This study is notable also for introducing a novel

analysis technique, the Iterative Data-driven Evolutionary Algorithm (IDEA), for automatically isolating regions of interest (e.g., PMdr) whose functional connectivity maximally correlates with an independent variable (e.g., impulsivity).

Reviews

Several NIA investigators have authored reviews on the topic of BOLD functional connectivity in health and disease (Corbetta, 2010; Fox and Greicius, 2010; Fox and Raichle, 2007; He et al., 2007a; Raichle, 2011; Raichle et al., 2001; Raichle and Mintun, 2006; Raichle and Snyder, 2007; Smyser et al., 2011; Zhang and Raichle, 2010).

Supplementary Material

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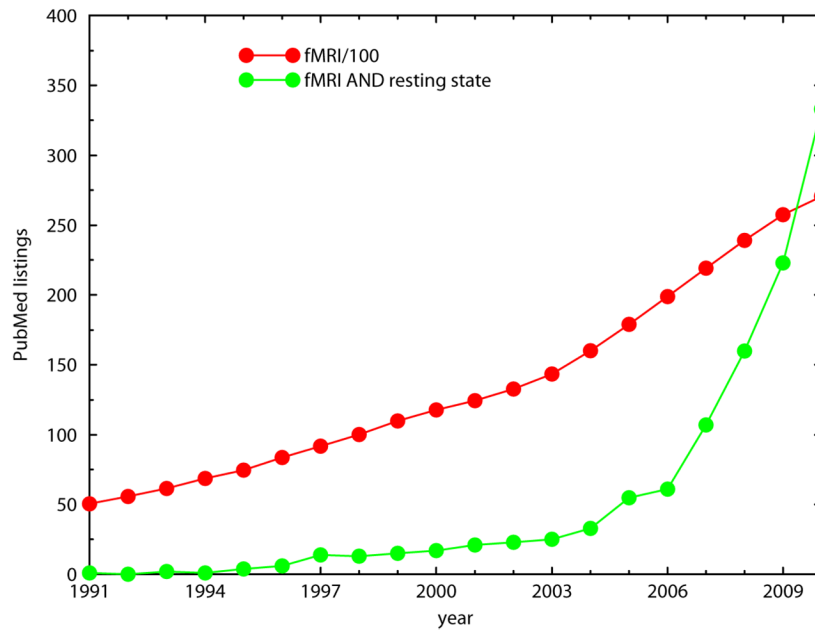


Figure 1. Graph of papers/year retrieved by a PubMed search using either “fMRI” or “fMRI AND resting state”. N.B.: The “fMRI” scale is compressed by a factor of 100. Resting state fMRI papers are appearing at an exponentially increasing rate. The current doubling time is a little less than 2 years.