

Low Frequency BOLD Fluctuations and Brain Functional Connectivity

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Functional connectivity imaging with BOLD fMRI

Functional connectivity refers to *correlations between spatially remote neurophysiological events* as described by Friston & Büchel. Functional connectivity is simply a statement about the observed correlations and does not imply how the correlation is mediated. Effective connectivity is closer to inter-neuronal connectivity as it refers to *influence that one neuronal system exerts over another* (Friston & Büchel). The difference between functional and effective connectivity is related to differences in the time and scale of the measurements; e.g. hemodynamics response function vs. spike trains. The following text focuses on the relationship between functional connectivity and low frequency fluctuations detected in resting state brain activity with BOLD fMRI.

Already the first blood oxygen level dependent (BOLD) magnetic resonance imaging at 4 T demonstrated a 2 % fluctuation in the image signal intensity at resting state between activations (Ogawa, *et al.* 1992). Weisskoff showed that actually the resting state BOLD signal frequency spectrum had 1/f characteristics in addition to cardiac and respiratory related signals (Weisskoff, *et al.* 1992). Biswal was the first to show that in the absence of external stimuli the low frequency BOLD signal oscillations are synchronous in bilateral primary motor cortices (Biswal, *et al.*, 1995). The detected correlation in the BOLD signals was regarded as functional connectivity.

Other research groups detected the BOLD oscillations later on (Mitra, *et al.* 1998, Xiong, *et al.* 1999). The spontaneous low frequency oscillations were later found in areas other than motor cortex as well. Some have even suggested that the fluctuation can map the functional cortices more extensively and concisely than single paradigm activation studies (Xiong, *et al.* 1999). The oscillations contain information about the integrity of the inter-hemispheric connectivity of functional areas (Li, *et al.* 2002, Lowe, *et al.* 2002).

Origin of low frequency BOLD fluctuation

Some have regarded the low frequency fluctuations as technical or physiological artifacts, and indeed, some of the low frequency power of BOLD signal can be regarded as such. Gradient drifts; cardiac/respiratory aliasing, SSFP-fluctuations and such do unavoidably produce signal variance in BOLD images (Zhao, *et al.*, 2000). However, the main source of low-frequency BOLD signal variance in the absence of stimuli and subject motion originates from regional physiological fluctuations (Biswal, *et al.*, 1995, Kiviniemi, *et al.*, 2005, Beckmann, *et al.*, 2005). In addition, several other modalities have detected the same low frequency phenomena without aliasing or other problems related to MR environment. In the following findings of low frequency, oscillations with three major modalities of brain function analysis are being presented. Table 1 will sum up recent observations of low frequency oscillations in the human brain.

EEG

Without high-pass filtering the baseline, EEG (i.e. the DC-level) has infraslow (ISO, 0.02 – 1 Hz) oscillations (Vanhatalo, *et al.* 2004). The power alpha, beta, delta, EEG rhythms actually follows the baseline infraslow EEG oscillations – the ISO produces a widespread synchronization of neuronal excitability (Vanhatalo, *et al.* 2004). In addition, the fluctuation of the EEG coherence is weighted towards slow frequencies of 0.02 Hz and below. The coherence fluctuations are local (10

mm) and more clearly present in intracranial than scalp EEG measurements (Bullock, *et al.* 1995). The coherence of EEG frequency bands (5-8, 13-20 and 20-35 Hz) fluctuates together, i.e. the bands are co-dependent of each other, as shown by Vanhatalo (2004) and Bullock and co-workers (1995).

Golanov, *et al.* (1996) detected oscillation of blood flow that was preceded by cortical electric bursts in deep isoflurane anesthesia. On the other hand, there are several studies showing no connection of localized cortical electric activity and vascular or metabolic fluctuations (Halsey & McFarland 1974, Vern, *et al.* 1988). The differences in findings may be related to use of anesthetics.

Slow EEG alpha power oscillations and BOLD signal fluctuations were found to correlate in distinct brain regions, some negatively and some positively (Goldman, *et al.* 2002). In 2003, several papers emerged detecting EEG power oscillations with regards to beta and alpha power oscillations and BOLD signal (Laufs, *et al.* 2003 a, b). The alpha power fluctuations correlate with inattention, whereas beta power oscillations are in concordance with conscious rest and default mode (Laufs, *et al.* 2003 b, Greicius, *et al.* 2004). EEG alpha power reduction is related to metabolic deactivation (Moosmann, *et al.* 2003).

Metabolic and blood gas oscillations

Astrocytes and neurons present slow oscillations in vitro and during each contraction cycle astrocytes secrete substances that are taken up by the neurons (Geiger 1963, Vern, *et al.* 1988). These volume oscillations are thought to reflect metabolic activity of the cell. A precise non-invasive NIRS-study noticed that both blood oxygenation and tissue cytochrome oxidation oscillate dominantly at low frequency (LF ~ 0.1 Hz) and at (VLF ~ 0.04 Hz) (Obrig, *et al.* 2000). The VLF oscillation detected in cytochrome oxidase levels follows the blood oxygenation oscillations with a lag of 4 seconds. The oscillations in deoxyhemoglobin and cytochrome oxidase are 10 times smaller in amplitude than the oxygenation level oscillations. The VLF rather than the LF oscillations may be the origin of functional connectivity measurements.

Another significant study showed that the CO₂-level of the brain precedes VLF BOLD oscillations. Both the blood oxygenation and flow follow the 2-mmHg amplitude pCO₂ -level oscillations with a lag of 6.3 seconds (Wise, *et al.* 2004). In addition, there is a connection between metabolic oscillations and both the EEG and BOLD signal oscillations (Moosmann, *et al.* 2003).

Vasomotor waves

Vasomotion controls both regional blood flow and systemic blood pressure most efficiently at low frequencies (< 0.1 Hz) (Zhang, *et al.* 2000). Carl Ludwig noticed in 1847 that blood pressure in dogs and horses presents slow waves at a rate of 1-5 / min. The waves were first detected in the human brain circulation during the 1950's (Hudetz, *et al.* 1998). The vasomotor waves are induced by myogenic activity (Hudetz, *et al.* 1998). Arterial walls present pressure dependent, multifocal contractions pointing to the autonomous origin of the oscillations.

The mechanism of controlling blood flow and pressure seem to be a result of integration of several control mechanisms and thus the control mechanism of vasomotor waves seem to be multimodal (Sokoloff, 1996). Sympathic and parasympathic or vascular nervous systems are likely candidates for the neurogenic oscillator (Zhang, *et al.* 2000). Metabolic and thermoregulatory aspects are slow to react and thus may induce fluctuations in only very low frequencies (Panerai, *et al.* 1998, Zhang, *et al.* 2000).

Blood oxygenation analyses tend to present a range of prominent frequencies rather than one specific frequency, c.f. Table 1. This is due to the presence of multiple oscillators affecting BOLD signal. There is evidence of at least two differently reacting spectral frequency ranges in blood pressured dynamics with a break point at about 0.02-0.025 Hz suggesting at least two control mechanisms (Wagner & Person 1994). The two control mechanisms seem to oscillate at separate

frequencies, faster neuromyogenic at 0.25–0.5 Hz and slower autonomic/metabolic at 0.02 – 0.2 Hz (Wagner & Person 1994, Panerai, *et al.* 1998, Zhang, *et al.* 2000).

Dora & Kovach (1981) have shown three different oscillatory rhythms in metabolism under alpha-chloralose. The phase relationship and frequency between the metabolic, blood flow and electrophysiological oscillations varies between these oscillations, suggesting a different origin and control mechanisms behind the oscillations.

Table 1. Studies of blood flow oscillation in humans. First author, year of publication, detection (technique), the measured signal (parameter) and fluctuation frequency (Hz) are mentioned.

Author	Year	Technique	Parameter	Frequency
Cooper	1966	Polarography	pO ₂	0.1
Livera	1992	NIRS	tot-Hb	0.1
Chance	1993	NIRS	Light absorption	0.1-5
Elwell	1996	NIRS	OxyHb,deoxyHb, tot-Hb	0.2
Elwell	1999	NIRS	OxyHb,deoxyHb, tot-Hb	0.08/0.22
Hoshi	1997/8	NIRS	OxyHb,deoxyHb, tot-Hb	0.01/0.008
Diehl	1991/5	TCD	MCA-FV	0.007/0.15
Giller	1999	TCD	MCA-FI	0.006-0.037
Hu	1999	TCD	MCA-FV	0.016-0.44
Kuo	1998	TCD	MCA-FV	0.016-0.44
Zhang	1998	TCD	MCA-FV	< 0.07-0.2
Bäzner	1995	TCD	MCA-FV	0.01-0.5
Blader	1997	TCD	MCA-FV	0.03-0.2
Mitra	1997	fMRI	BOLD	0.1
Biswal	1995	fMRI	BOLD	< 0.08
Biswal	1997	fMRI	BOLD	0.02-0.14
Lowe	1998	fMRI	BOLD	< 0.08
Kiviniemi	2000	fMRI	BOLD	0.03-0.1
Li	2002	fMRI	BOLD	0.04 - 0.23
Moosmann	2003	fMRI+NIRS+EEG	BOLD+deoxyHb+ α	0.2-0.3 \square
Laufs	2003	fMRI+EEG	BOLD+ α + β	0.022
Wise	2004	TCD+fMRI+capnograph	MCA-FV+BOLD+pCO ₂	<0.05

NIRS = near-infrared spectroscopy, TCD = transcranial Doppler ultrasound. pO₂ = partial oxygen tension, Oxy = oxygenated, deoxy = deoxygenated, tot = total hemoglobin (Hb). MCA = middle cerebral artery, FV = flow velocity and FI = flow index, α = alpha and β = beta EEG rhythms, pCO₂ = partial carbon dioxide tension. \square) The frequency calculated from an image.

BOLD signal – a mixture of multiple oscillators

Resting state connectivity measurements of the brain that utilize BOLD signal are *de facto* reflecting blood oxygenation similarity across the brain, not directly neuronal coherence. DeLuca and co-workers (2005) showed that perfusion data could map the same brain networks as BOLD signal data. Hypercapnia and sevoflurane anesthesia both abolish interregional functional connectivity whereas intravenous (i.v.) anesthetics enhance it (Biswal *et al.* 1997, Peltier *et al.*, 2005, Kiviniemi, *et al.*, 2005). Hypercapnia and sevoflurane increase blood pressure and flow, and reduce < 0.1 Hz vasomotor waves (Hudetz *et al.*, 1992). I.v. anesthetics on the other hand reduce blood pressure and increase <0.1 Hz vasomotor waves. Since BOLD signal connectivity arises from < 0.1 Hz fluctuations the induced alterations in the power of low frequency fluctuations also alters connectivity measurements (Cordes *et al.*, 2001).

The reason why the BOLD signal fluctuation in low frequency is specific to areas known to have functional connections across the brain is not yet clear. Biswal showed that the BOLD signal originating from within the primary motor areas has clearly more correlation than non-functionally

connected regions. His original idea was that oscillations could be carrying messages between functional areas: "...like amplitude and frequency modulated radio waves". If the vasomotor fluctuations were the only origin of low frequency BOLD variability then these signal sources should be presenting more global areas, probably more close related to vascular territories. However this is not the case (Kiviniemi, *et al.*, 2003, Beckmann, *et al.*, 2005, DeLuca, *et al.*, 2005).

EEG power and pCO₂ – level related BOLD oscillations seem to be located in unique functional areas with correlation to functional resting state networks (Wise *et al.*, 2004, Laufs 2003, Golmann 2002, Moosmann *et al.*, 2004). The obvious question is why are the signal sources of resting brain activity clearly following functional neuroanatomy and not vascular territories (Kiviniemi *et al.*, 2003, Greicius *et al.*, 2004, Beckman 2005, DeLuca, *et al.* 2005, Fransson 2005).

The authors opinion is that the temporal behaviour of the BOLD signal is a sum of effects induced by neuronal activity, autonomous blood flow control inside the central nervous system, metabolism, vasomotor waves, etc. In functionally connected signal sources detected with BOLD the vasomotor waves function as a temporal contrast within the grey matter. Hypercapnia and sevoflurane abolish this temporal contrast and i.v. anesthesia enhances it.

Neuronal activity as a strong modulator of blood oxygenation set it's fingerprints on the BOLD signal in addition to the vasomotor waves. The resulting temporal oxygenation pattern detected as BOLD signal is a regionally specific interference pattern. When interregional neuronal activity is affecting this interference pattern, it enables the detection of interregional correlation of brain networks. Hypercapnia and sevoflurane abolishes the fingerprints of neuronal activity from the BOLD signal with increasing the flow by a ceiling-effect.

Methods of analyzing functional connectivity

The non-deterministic resting state BOLD signal is complex and unpredictable due to interference of multiple oscillators. Thus the analysis methods should be more data than hypothesis driven. Statistical analysis yields most accurate results in complex or chaotic data (Kiviniemi, *et al.* 2003). Data-driven methods like independent component analysis (PCA or ICA, respectively) have proven to be important tools in analyzing resting state activity. FSL based MELODICA (Beckmann, *et al.* 2001) and GIFT by Vince Calhoun have enabled very solid noise differentiation, signal source estimation and population based analysis of resting state activity.

Originally the functional connectivity measurements of Biswal (as well as the conventional BOLD activation) data analysis were based on region of interest or seed voxel based correlations. One of the distinctive strengths of this method is the exact knowledge on the features, which are used in detecting functionally connected regions. More advanced extensions like regional heterogeneity and seed voxel based self-organizing maps have emerged (Zang, *et al.*, 2005).

An early method of detecting periodic BOLD activations or fluctuations was FFT (Bandettini *et al.*, 1996, Kiviniemi, *et al.* 2000). Nowadays autoregressive and spectral coherence analysis (Sun *et al.* 2005) seems very promising with regards to phase delay analysis of different fluctuations answering questions what is the temporal order of different oscillators. FFT power fit derivatives like fractal dimension analysis and Hurst exponent offer powerful tools for the characterization of BOLD signal variability without being constricted into one specific frequency (Bullmore, *et al.*, 2001, Welch, *et al.*, 2005). These methods enable the analysis of the combined effects of different oscillator simultaneously and enable the analysis of fluctuation wavelets rather than rigid periodicity.

Feature space and multi dimensional scaling (MDS) represent a strongly emerging new field to cover the dimensionality problem often troubling analytics (Friston & Büchel, Thirion, *et al.* 2005). Canonical variate analysis can detect functional connected activity with normal statistical inferences with regards to the activity without making assumptions about the spatial correlations (Friston & Büchel). These methods have promising capabilities towards extending functional resting state analysis towards clinical applications.

Beyond present clinical imaging

Li was the first to show changes in resting state BOLD signal connectivity in Alzheimers disease (Li et al., 2002). Lowe soon also detected reduced connectivity in MS (Lowe, et al., 2002). Some findings of reduced connectivity have emerged on ADHD and Asperger's disease. A very significant set of findings was produced by Greicius, *et al.* (2003 & 2004), showing that a) resting state fluctuations of the brain are involved in a default-mode network engaged in surveillance and control of the resting brain b) importantly the early Alzheimer patients showed detectable differences in default mode rest activity.

Beckmann was able to detect several brain networks with ICA of BOLD data. They further showed that also continuous arterial spin labeling perfusion data can be used in detecting the same networks repeatedly when analyzed with ICA (DeLuca et al., 2005). The detected networks have been shown to be involved in answering questions like what were the observed phenomena, where are they detected in space and what do the observations mean to the observer. The analysis of these networks may well be of clinical use in diseases not evident with present imaging methods.

Fox, et al., as well as Fransson have showed during 2005 that the resting state networks have inversely correlating components, i.e. opposed phase networks in distinct regions of the brain. These networks are involved in multiple tasks of introspection, mentalization, and controlling inner milieu stability as well as surveillance of the external interior. Our group has detected significant alterations in these resting state networks and their inversely correlated components in a cohort study of psychiatric patients. Welchew and co-workers (2005) have pointed out profound changes functional connectivity with MDS in schizophrenics subjects. Increasing understanding of fractional noise and fractal dimension properties of brain oxygenation can take us beyond our present understanding of functional connectivity and it's relation to brain patho-physiology (Maxim et al., 2005).

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