Implications of cortical balanced excitation and inhibition, functional heterogeneity, and sparseness of neuronal activity in fMRI

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Abstract

Blood-oxygenation-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) studies often report inconsistent findings, probably due to brain properties such as balanced excitation and inhibition and functional heterogeneity. These properties indicate that different neurons in the same voxels may show variable activities including concurrent activation and deactivation, that the relationships between BOLD signal and neural activity (i.e., neurovascular coupling) are complex, and that increased BOLD signal may reflect reduced deactivation, increased activation, or both. The traditional general-linear-model-based-analysis (GLM-BA) is a univariate approach, cannot separate different components of BOLD signal mixtures from the same voxels, and may contribute to inconsistent findings of fMRI. Spatial independent component analysis (sICA) is a multivariate approach, can separate the BOLD signal mixture from each voxel into different source signals and measure each separately, and thus may reconcile previous conflicting findings generated by GLM-BA. We propose that methods capable of separating mixed signals such as sICA should be regularly used for more accurately and completely extracting information embedded in fMRI datasets.

Keywords

independent component analysis; neuroimaging; general linear model; neurovascular coupling; hemodynamic response function; magnetic resonance imaging

1. Introduction

Blood-oxygenation-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) has been used to investigate human brain functional organization for more than 20 years. However, findings from different fMRI studies are not always consistent (Mayberg, 2014; Parens and Johnston, 2014). For example, some studies find that BOLD signals from the so-called default mode network (DMN) or task-negative network at the medial portion of

the brain negatively correlate with the BOLD signals from the so-called task-positive network at the lateral part of the brain (Carbonell et al., 2011; Fox et al., 2005). However, some other studies report that such anti-correlations are in part artificially introduced during preprocessing of fMRI datasets (Anderson et al., 2011; Chai et al., 2012; Murphy et al., 2009). Still others find that these anti-correlations are dependent on brain states or task conditions (Piccoli et al., 2015; Spreng et al., 2014). In this paper, we propose that some of these controversial findings in fMRI are probably due to several closely related brain properties, including balanced excitation and inhibition (E/I) and functional heterogeneity (Isaacson and Scanziani, 2011; Okun and Lampl, 2008), the limited spatial and temporal resolutions of fMRI, and the limited sensitivity and specificity of general-linear-model based analysis (GLM-BA) commonly used in fMRI studies.

To our knowledge, several brain properties such as balanced E/I are usually not explicitly considered in published fMRI studies. The aims of this paper are to attract the attention of fMRI investigators to these fundamental brain properties, initiate a discussion on their implications in fMRI, and consider optimal approaches for addressing them during analyzing and interpreting BOLD signals in order to improve the sensitivity and specificity of fMRI and reduce conflicting findings. We will first briefly introduce three closely related brain properties, i.e., balanced E/I, functional heterogeneity, and sparseness of neuronal activity, then discuss their potential implications in BOLD signal changes, and finally discuss a potential approach for addressing these properties in the analysis and interpretation of BOLD data.

2. Three closely related brain properties

2.1. Balanced E/I

Balanced E/I refers to the electrophysiological findings that excitatory and inhibitory synaptic activities always associate with each other at the levels of individual neurons and microcircuits in the cortex during both the resting condition and task performance (Isaacson and Scanziani, 2011; Okun and Lampl, 2008). Within any cortical region, about 20% of all neurons are GABAergic inhibitory interneurons and 80% excitatory pyramidal neurons (Druga, 2009). The interneurons and pyramidal neurons form feedforward and feedback inhibitory circuits, the building blocks of the cortex (Haider et al., 2013; Isaacson and Scanziani, 2011). Feedforward inhibition from broadly tuned inhibitory interneurons (e.g., driven by the thalamus) restricts receptive fields and enhances representation of contrast in pyramidal neurons (Li et al., 2014). Feedback inhibition mediates inhibitory responses among adjacent pyramidal neurons (Ren et al., 2007; Silberberg and Markram, 2007). Furthermore, the inhibitory interneurons form extensive synapses onto adjacent pyramidal neurons, as if to exert a 'blanket of inhibition' (Fino et al., 2013; Fino and Yuste, 2011; Inan et al., 2013; Karnani et al., 2014; Markram et al., 2004; Packer and Yuste, 2011). Therefore, even though inhibitory neurons are fewer than excitatory neurons in the cortex, they are powerful minorities that refine the response tuning of excitatory neurons, dominate microcircuit activities, and control information processing in the cortex (Haider et al., 2013; Li et al., 2014; Mateo et al., 2011; Miller, 2003; Okun and Lampl, 2008; Ren et al., 2007). It should be noted that balanced E/I does not mean the cortex maintains a constant E/I ratio;

the E/I ratio in fact varies dynamically in different cortical regions and in the same region at different times, either during the resting condition or during different tasks (Isaacson and Scanziani, 2011).

2.2 Functional heterogeneity

Functional heterogeneity is another cortical property. The property of balanced E/I inevitably leads to different functional activities (i.e., activation vs. deactivation) among adjacent neurons. However, functionally heterogeneous neurons at adjacent locations may not always show mutual inhibition. Therefore, functional heterogeneity and balanced E/I are closely related but different properties in the brain. Electrophysiological studies have found that intermixed neurons in the same regions, including both the primary sensory and higher order association cortex, may have different functional activities (Horton and Adams, 2005; Isaacson and Scanziani, 2011; Ohki et al., 2005; Perin et al., 2011; Popivanov et al., 2014; Rothschild et al., 2010; Stettler and Axel, 2009; Swindale, 1998; Xu et al., 2013a). For example, the primary visual cortex contains a so-called "polymap", i.e., several overlapping maps, each responsive to a unique visual property, such as edge orientation, direction of motion, and spatial location and frequency. The primary auditory and olfactory cortices show a "salt and pepper" like organization (Bandyopadhyay and Hablitz, 2007; Isaacson and Scanziani, 2011; Poo and Isaacson, 2009; Rothschild et al., 2010; Stettler and Axel, 2009). In the prefrontal cortex (PFC), neurons responsive to any specific stimulus property constitute a minority in any region, with a relatively higher density at some locations, but distributed in most or the entire PFC, without any abrupt edges (Fuster, 2009). For example, both reward- and working memory-related neurons exist in the dorsolateral PFC, medial orbitofrontal cortex (OFC), and other PFC regions, although they are not evenly distributed in these regions. More reward-related neurons concentrate in the OFC, while more working memory-related neurons reside in the lateral PFC (Ichihara-Takeda and Funahashi, 2007, 2008; Wallis and Miller, 2003). Therefore, intermixed neurons with heterogeneous functional activities exist in each PFC region, while different neuron types may be concentrated in different regions (Chafee and Goldman-Rakic, 1998; Donovan et al., 2013; Funahashi, 2013; Verduzco-Flores et al., 2009). Thus, different PFC regions show more or less common functional activities, i.e., overlap of functional networks, but each region may show a greater activity related to some central processes relative to others (Fuster, 2009).

2.3. Sparseness of neuronal activity

Sparseness of neuronal activity is another cortical property related to balanced E/I (Barth and Poulet, 2012; Wolfe et al., 2010). Electrophysiological studies find that any cortical neuron is only responsive to a few stimuli among all inputs from the environment (i.e., lifetime sparseness) (Tolhurst et al., 2009), and that only a small portion of the whole neuronal population in any cortical region exhibits activity at any instant (i.e., population sparseness), while most neurons remain silent, regardless of resting condition or task performance (Histed et al., 2009). This sparseness of neural activities is probably mediated by the inhibitory interneurons in the cortex. It has been found that the inhibitory interneurons contribute to the so-called "iceberg effect", i.e., pyramidal neurons having narrower spiking receptive fields than subthreshold receptive fields (Isaacson and Scanziani, 2011; Priebe and Ferster, 2008). For example, in the primary somatosensory barrel cortex of

behaving mice, all recorded layer 2/3 pyramidal neurons show rapid depolarization in response to whisker stimulation, but only 10% of them show spikes (Crochet et al., 2011). In the primary auditory cortex of awake rats, acoustic stimuli typically elicit increased firing rates in less than 5% of all neurons at any instant (Hromadka et al., 2008).

3. Potential implications of these brain properties for fMRI

3.1. Heterogeneous neural activity in each voxel

A typical voxel in the cortex extending 3-5 mm in each dimension contains hundreds of thousands of neurons (Druga, 2009; Logothetis, 2008; Roth and Dicke, 2012). The three cortical properties discussed above indicate that neural activities in the same voxels or brain regions are highly heterogeneous, as suggested by findings from numerous studies (Chafee and Goldman-Rakic, 1998; Donovan et al., 2013; Funahashi, 2013; Fuster, 2009; Verduzco-Flores et al., 2009). For example, Bell et al. assessed the relationships between neural activity and BOLD signal in the inferior temporal cortex in two monkeys. They first used fMRI to delineate brain regions showing significant BOLD responses to different categories of visual stimulus including face, body parts, objects, and environment scenes, then used microelectrodes to record single unit activity in each of these regions (Bell et al., 2011). They found that neurons activated and deactivated by each stimulus category were distributed throughout the entire recorded inferior temporal region, instead of being restricted within a specific area. However, within a region defined by fMRI with a specific category of visual stimulus, more neurons were activated then deactivated by stimuli in the same category, whereas more neurons were deactivated than activated by stimuli in other categories. For example, in the fMRI face region, more neurons were activated than deactivated by face, whereas fewer neurons were activated than deactivated by objects, other body parts, and scenes. Another study recorded single units from the posterior cingulate cortex (CGp) and lateral intraparietal area (LIP) in two monkeys during two attention-demanding tasks (Hayden et al., 2009). The CGp and LIP are among regions of the DMN and task-positive network, respectively. They often show reduced and increased, respectively, BOLD signal during attention-demanding tasks. Microelectrode recordings found that 35% of recorded neurons in the CGp were deactivated but only 9.4% activated during attention-demanding tasks. On the other hand, 20% of LIP neurons were activated and 7.4% deactivated. Therefore, both CGp and LIP showed heterogeneous task-related neuronal activities. Furthermore, more than 50% of recorded neurons in the CGp and LIP did not show significant changes in activity, consistent with the cortical property of sparseness of neural activity.

The three brain properties allow us to make five conclusions regarding neural activities in each voxel: 1) Some neurons may increase firing while others decrease firing simultaneously (i.e., balanced E/I) in each voxel at any instant of a resting condition or task performance. 2) Intermixed neurons in each voxel may show different timecourses of firing (i.e., functional heterogeneity). 3) Most neurons in each voxel do not increase firing at any instant (i.e., sparseness of neuronal activity). 4) Different voxels may show different ratios of activated (i.e., increased firing) and deactivated (i.e., reduced firing) neurons, because of variable E/I ratios in different voxels. 5) The ratio of activated and deactivated neurons (i.e.,

E/I ratio) in the same voxel may change dynamically during resting or different task conditions. These balanced and heterogeneous features of neural activities in each voxel, as determined by the three brain properties, have significant implications in relationships between neural activity and BOLD signal (i.e., neurovascular coupling) and hemodynamic response function (HRF).

3.2. Neurovascular coupling and HRF

Neurovascular coupling is one of the most important issues for properly interpreting fMRI data (Logothetis, 2008). It refers to the relationship between BOLD signal and neuronal activity, including both spiking and synaptic activity. For assessing neurovascular coupling, investigators have performed electrophysiological recording and fMRI of animal brains simultaneously, and then analyzed correlations between changes in BOLD signal and single and/or multi-unit firing rates and local field potentials (LFPs) (Hillman, 2014; Logothetis et al., 2001). Multiple studies found that neuronal activation and deactivation increased and decreased BOLD signal, respectively (Devor et al., 2007; Ekstrom, 2010; Goense et al., 2012; Logothetis, 2008; Shmuel et al., 2006), although non-neural factors such as astrocytes and local vascular features might also affect BOLD signal (Ekstrom, 2010; Hillman, 2014; Howarth, 2014). However, findings on the exact relationships between BOLD signal and other measures of neural activity were not fully consistent among different studies (Boynton, 2011; Nir et al., 2008; Renvall et al., 2014). Some studies found that neuron firing rates correlated with BOLD signal (Boynton, 2011; Nir et al., 2008), while others found that LFP but not firing rates correlated with BOLD signal and therefore proposed that BOLD signal reflected synaptic activities instead of neuron spiking (Logothetis, 2002; Logothetis et al., 2001; Viswanathan and Freeman, 2007).

There are 25,000 to 30,000 neurons/mm^3 in the cortex (Roth and Dicke, 2012), and each voxel may have more than ten thousand neurons, even for high-resolution fMRI of an animal brain (e.g., ~500 μm in each dimension). The three above-mentioned brain properties allow us to make two predictions regarding neurovascular coupling, if, as reported in multiple studies (Devor et al., 2007; Ekstrom, 2010; Goense et al., 2012; Logothetis, 2008; Shmuel et al., 2006), neuronal activation and deactivation indeed cause increases and decreases, respectively, in BOLD signal. First, different neurons in the same voxel will show different correlations between their firing rates and BOLD signal and thus different neurovascular coupling, e.g., some may show positive while others show negative correlations due to balanced E/I and functional heterogeneity. Second, neurovascular coupling may vary across voxels due to different E/I ratios in different voxels, and in the same voxels at different instants due to different E/I ratios during different tasks. These two predictions are supported by findings of variable neurovascular coupling from several animal studies (Amit and Romani, 2007; Bartolo et al., 2011; Boorman et al., 2010; Boynton, 2011; Ekstrom, 2010; Maier et al., 2008).

In one study, awake monkeys showed consistent changes in BOLD signal and neural activity (e.g., increases in both) in the V1 cortex during regular visual stimulation, but different changes in the two measures (i.e., reduced BOLD signal but not neural firing) during perception suppression (Maier et al., 2008). In another study, relative to visual single-

grating stimulation, plaid pattern stimulation increased BOLD signal and the firing rates of some V1 neurons in awake monkeys but simultaneously decreased firing of other neurons, probably due to visual cross-orientation inhibition (Bartolo et al., 2011). In a third study, Boorman et al (2010) recorded neuron and BOLD responses in the rat barrel cortex to electrical stimulation of the contralateral whisker pad. Their findings indicate that more neurons are activated than deactivated in regions showing increases in BOLD signal and more neurons deactivated than activated in regions showing decreases in BOLD signal (Boorman et al., 2010). Therefore, balanced E/I and functional heterogeneity in the brain probably contribute to the different findings in neurovascular coupling from different studies. Based on these two brain properties, we propose that it is probably not a valid approach to assess neurovascular coupling by correlating changes in BOLD signal and single or multi-unit firing rates from the same voxel without considering the E/I ratio across the entire neuron population in the voxel, and that the previous conclusion that spiking does not contribute to BOLD signal is probably not valid (Logothetis, 2002; Logothetis et al., 2001), because these studies have not assessed the E/I ratio among different neurons.

Since the delay, shape, and amplitude of the HRF are dependent on neurovascular coupling, the above-discussed location and task dependent neurovascular coupling predicts that the HRF is probably variable among different voxels and in the same voxel during different tasks. This variability has been reported and discussed by several studies (Buxton, 2012; Handwerker et al., 2012; Handwerker et al., 2004). Therefore, we propose that balanced E/I and functional heterogeneity in the brain contribute to the location and task dependent variability of the HRF, in addition to other factors, such as local vascular features, discussed in previous studies (Handwerker et al., 2012). The variable neurovascular coupling and the HRF complicate the interpretation of BOLD signal changes.

3.3. Task-related changes in BOLD signal

As discussed above, both activation and deactivation are highly likely to exist concurrently in each voxel during either resting or task conditions, and this concurrent co-localized activation and deactivation (CCAD) complicates neurovascular coupling and the HRF. BOLD signals related to opposite changes in neural activities in the same voxel may cancel each other, and therefore BOLD signal changes from each voxel probably reflect changes in difference (or ratio) between CCAD, not in activation or deactivation alone (Fig. 1). A voxel may not show any BOLD signal change if its difference in CCAD does not change, even though individual neurons may change activity significantly. It may express a greater BOLD signal if its neuron population reduces total deactivation without an increase in total activation. Fig. 1 shows predicted potential relationships between BOLD signal and CCAD from a voxel in four (i.e., S1-4) of many possible scenarios. To support our point, we purposely selected scenarios of smaller activation and deactivation in task condition B (i.e., TB) relative to A (i.e., TA). However, TB may exhibit a smaller, greater, or equal positive BOLD signal as depicted in S1, S2, and S3, respectively, and a smaller negative BOLD signal in S4, relative to TA. Fig. 1 clearly demonstrates that BOLD signal changes depend not only on activation but also on deactivation, and that a greater BOLD signal is not always due to a greater activation, but may be due to a smaller deactivation (e.g., Fig.1 S2). Therefore, increases or decreases in BOLD signal at one task condition relative to another

condition do not reliably indicate a greater activation or smaller deactivation at either task condition.

4. An approach for addressing these brain properties

4.1. General-linear-model-based-analysis (GLM-BA)

FMRI studies traditionally employ a univariate analysis, i.e., general-linear-model-based-analysis (GLM-BA). It treats the BOLD signal mixture related to different neuronal activities (e.g., CCAD) from each voxel as an independent measure, and does not separate this BOLD signal mixture into different components (Logothetis, 2008; Serences and Saproo, 2012; Xu et al., 2013a). Therefore, GLM-BA is blind to balanced E/I and functional heterogeneity within a voxel. It may incorrectly report a greater brain activation in TB relative to TA of Fig. 1, when it detects a greater BOLD signal in TB, even though TB may actually have a smaller activation and deactivation, as depicted in Fig.1 S2. Therefore, GLM-BA has a limited specificity, which may lead to misinterpretation of reduced deactivation as increased activation. Furthermore, GLM-BA may show no difference in BOLD signal changes between TA and TB even though TB may actually have a smaller activation and deactivation than TA, as depicted in Fig. 1 S3. Therefore, GLM-BA has a limited sensitivity in detecting task-related changes in neuronal activity, and fMRI studies using GLM-BA may underestimate task-related changes in neural activity between task conditions and generate false negative results (Logothetis, 2008; Serences and Saproo, 2012; Xu et al., 2013a). The limited specificity and sensitivity of GLM-BA may contribute to the inconsistent data mentioned earlier. Therefore, analytical methods capable of separating a BOLD signal mixture related to CCAD in a voxel are desirable because they may have a greater sensitivity and specificity than GLM-BA in analyzing a BOLD time series. In this regard, several recent studies used at least three different methods for assessing concurrent co-localized BOLD signals during either a resting condition or task performance (Braga et al., 2013; Xu et al., 2013b; Yan et al., 2011; Yeo et al., 2013). One study used Connected Iterative Scan (CIS), a graph-theoretic clustering algorithm originally developed for analyzing community overlaps in inter-personal social networks, and reported an overlap of DMN and task-positive network during a resting condition (Yan et al., 2011). Another study used Latent Dirichlet Allocation (LDA), originally developed for text mining, and reported overlaps of multiple functional networks (FNs) during a resting condition (Yeo et al., 2013). Several other studies used a method called spatial independent component analysis (sICA). We will focus on sICA in the following text, because it is a more popular approach for assessing brain FNs in fMRI studies relative to the first two methods, and multiple recent fMRI studies have used sICA to separate BOLD signal mixtures from the same voxels and consistently reported extensive overlaps of FNs.

4.2. Spatial independent component analysis (sICA)

Independent component analysis (ICA) was originally developed for extracting hidden, unknown source signals from observed signal mixtures using higher-order statistics (Beckmann, 2012; Calhoun and Adali, 2012; Calhoun et al., 2009; Comon, 1994; McKeown et al., 1998b). In fMRI, sICA assumes that the BOLD signal from each voxel represents a linear mixture of source signals and separates it into spatially independent components (ICs)

(Calhoun and Adali, 2012; Calhoun et al., 2002; Calhoun et al., 2009; McKeown et al., 1998a; McKeown et al., 1998b; McKeown and Sejnowski, 1998). In one of its earliest applications in fMRI, sICA separated the BOLD signal from one voxel into as many as six ICs (McKeown et al., 1998b). This unique capacity has been used to separate artifacts from signals in order to de-noise fMRI data (Aron and Poldrack, 2006; Beckmann, 2012; Brooks et al., 2013; Griffanti et al., 2014; Tohka et al., 2008; Yakunina et al., 2013). Over the last 15 years, sICA has arguably become one of the two most popular methods (along with seed-based approaches) for studying FNs, because it groups all voxels with synchronized source signals into one FN (Beckmann, 2012; Calhoun and Adali, 2012; Calhoun et al., 2009; Comon, 1994; McKeown et al., 1998b). Some studies describe spatial overlap of two or more FNs, indicating that sICA splits the BOLD signal from each voxel within overlapping regions into two or more FNs (Calhoun et al., 2008; Domagalik et al., 2012; Kim et al., 2009a; Kim et al., 2009b; Menz et al., 2009; St Jacques et al., 2011; van Wageningen et al., 2009; Wu et al., 2009; Zhang and Li, 2012). Very recently, we and three other groups have used sICA to systematically assess FN overlaps (Beldzik et al., 2013; Braga et al., 2013; Geranmayeh et al., 2014; Leech et al., 2012; Xu et al., 2014a; Xu et al., 2013a; Xu et al., 2013b; Yeo et al., 2013), and have consistently demonstrated: 1) that FNs often overlap with each other extensively, 2) that overlapping FNs may show concurrent but opposite task-related modulation (e.g., activation vs. deactivation), and 3) that the overlapping opposite modulations revealed by sICA may cancel each other and not show any modulation in GLM-BA. We have proposed that overlapping FNs with opposite time courses probably reflect CCAD existing in each voxel as stipulated by balanced E/I and functional heterogeneity in the brain.

4.3. Novel features of brain functional organization revealed by sICA

SICA may have a better specificity and sensitivity than GLM-BA and show novel feature of brain functional organization not revealed by GLM-BA such as extensive overlaps of FNs with opposite timecourses of task-related activities (Beldzik et al., 2013; Costumero et al., 2014; Domagalik et al., 2012; Xu et al., 2014b; Xu et al., 2015), due to its unique capacity of separating intermixed signals. In one of our recent studies, a GLM-BA revealed task-related increases, decreases, and no-changes in BOLD signal in separate brain regions. These findings are consistent with data from most fMRI studies that used GLM-BA of separated brain regions showing task-positive, negative, or absence of changes in activity. However, sICA revealed extensive overlaps of FNs showing task-related increases (i.e., task-positive FNs), decreases (i.e., task-negative FNs), and absence of changes (i.e., task-neutral FNs) in activity. Although the task-positive FNs covered most or all brain regions during highly demanding or complex cognitive tasks, so did the task-negative FNs and task-neutral FNs (Xu et al., 2015). Therefore, these FNs showed different task-related concurrent modulations, overlapped with each other, and covered almost the same brain regions, instead of being segregated among brain regions as revealed by the GLM-BA. These findings of sICA are consistent with the evidence that neurons showing task-related activation, deactivation, or no change in activation are intermixed with each other in the same brain regions (Bell et al., 2011; Borra et al., 2010; Fuster, 2009). They are also consistent with the three brain properties discussed above: balanced E/I, functional heterogeneity, and sparseness of neuronal activity. Therefore, findings from sICA and GLM-BA present a

different framework of brain functional organization, i.e., overlapped and extensively distributed vs. segregated and restricted functional activities with different timecourses. The novel framework revealed by sICA should be further investigated.

The potentially greater sensitivity and specificity of sICA relative to GLM-BA may provide a novel opportunity for reconciliation of inconsistent findings of previous fMRI studies using GLM-BA, including the example presented at the beginning of this review. The property of balanced E/I in the brain predicts that anti-correlated FNs should always exist in the same and/or different brain regions. This notion is supported by the sICA finding of overlapping FNs with opposite timecourses. However, BOLD signals from different voxels do not have to show anti-correlations because they represent mixtures of different source signals including anti-correlated signals. Therefore some studies using GLM-BA may show anti-correlations between BOLD signals while some other studies may not. The novel findings from sICA along with the balanced E/I in the brain indicate to us that the opposite modulations of task-related timecourses of FNs in the same and/or different brain regions (e.g., the medial vs. lateral prefrontal cortex) may reflect balanced E/I among different FNs as discussed in a recent publication (Leech et al., 2014). Therefore, balanced E/I exists not only at the level of neurons and microcircuits, as revealed by electrophysiological studies, but also at the level of large-scale networks of the whole brain.

Conclusion

Balanced E/I, functional heterogeneity, and sparseness of neuronal activity are basic brain properties. They complicate neurovascular coupling and the HRF and the interpretation of task-related changes in BOLD signal. Thus, they probably contribute to inconsistent findings in fMRI studies using GLM-BA. Therefore, to understand brain functional organization, it is probably not adequate to use GLM-BA alone in fMRI studies. SICA has been used in fMRI studies for more than 15 years mainly due to its data-driven and model-free features. These studies usually do not describe FN overlaps and do not explicitly assess concurrent co-localized source signals from the same voxels. The recent sICA findings of overlapping FNs with different timecourses demonstrated the potential capacity of sICA for separating mixed signals in the same voxels, for reconciling extant conflicting fMRI findings, and for revealing novel features of brain functional organization. We strongly recommend that sICA or any other methods capable of separating signal mixtures should be regularly employed in addition to GLM-BA for more completely extracting information embedded in fMRI data.

Acknowledgments

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Highlights

1. The cortex is heterogeneous in function and maintains a balance of excitation and inhibition.

2. These properties indicate concurrent neuron activation and deactivation in the same voxels.

3. Either increased neuron activation or reduced deactivation may increase BOLD signal.

4. Traditional fMRI analysis may misinterpret reduced deactivation as increased activation.

5. Independent component analysis may reconcile conflicting findings of traditional analysis.
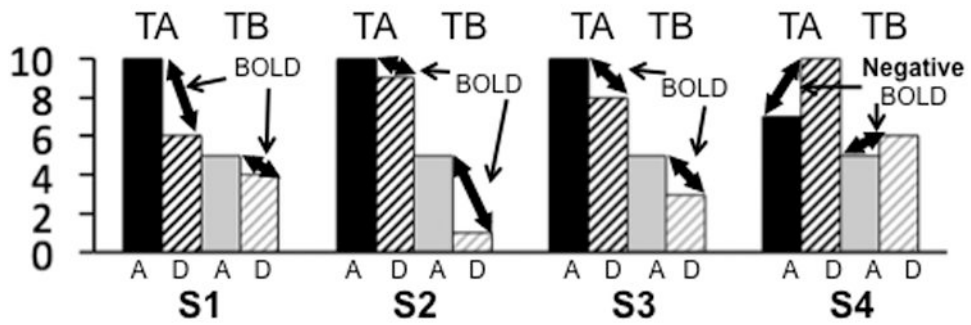
Fig. 1.
Potential relationships between BOLD signal and neuronal activity in a voxel. Solid and dashed columns represent total activation (A) and deactivation (D), respectively, in a voxel in task condition A (TA, black) and B (TB, gray), in arbitrary units. BOLD signal sizes depend on differences between A and D, not A or D alone. S1-4 shows four possible scenarios. While TB shows a smaller activation and deactivation than TA in each scenario, it does not always show a smaller BOLD signal.