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The absence of task-related increases in BOLD signal does not equate to absence of task-related brain activation

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Abstract

Most fMRI studies employ general-linear-model-based analyses (GLMBA) of BOLD signal changes to identify regions that are active (or not) during specific cognitive processes. However, alternate analytic approaches (like independent component analysis) may identify more complex patterns of activation, including in regions not implicated in GLM-BA of the same data. In our opinion, fMRI findings revealed by a GLM-BA cannot exclude any brain regions from contributing to specific cognitive processes.

Keywords

General Linear Model; Spatial Independent Component Analysis; Balanced excitation and inhibition; Functional heterogeneity

Most studies use general-linear-model-based analysis (GLM-BA) to identify brain regions whose activations during functional magnetic resonance imaging (fMRI) may contribute to specific cognitive processes. However, GLMBA may, due to the complexity of brain

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functional organization, under-estimate the regional brain contributions relating to performance of such processes. In this paper, we will discuss how two fundamental properties of the brain (i.e., functional heterogeneity and balanced excitation and inhibition) may limit the sensitivity and specificity of GLM-BA, and why combining GLM-BA with a multivariate approach, i.e., spatial independent component analysis (sICA), will typically reveal more brain functional activity than GLM-BA alone. We hope that this discussion will provide a theoretical framework for future studies explicitly acknowledging the limitations of GLM-BA findings, and that both GLM-BA and sICA will be used to interrogate fMRI data for a more complete understanding of brain functional activity. To highlight these points, we will focus on a recently published article (Donoso et al., 2014).

To investigate the architecture of reasoning processes in the prefrontal cortex (PFC), Donoso et al (Donoso et al., 2014) used fMRI to measure blood-oxygenation-level-dependent (BOLD) signal in the PFC while healthy participants performed a visual task. This task required the participants to select a response strategy, evaluate the reliability of selected and alternate strategies based on feedback, and create new response strategies if necessary. By using a GLM-BA to interrogate acquired BOLD timeseries, they found that the reliability of the selected and alternative strategies correlated differently with task-related BOLD signal changes in the medial and lateral PFC, but did not correlate with BOLD signal in any other PFC regions. They concluded that the medial PFC evaluated the selected strategy whereas the lateral PFC concurrently evaluated alternative strategies. In our opinion, their fMRI findings indicate that the medial and lateral PFC do contribute differently to the evaluations of selected vs. alternate strategies. However, the approach employed cannot exclude potential contributions of the medial PFC and other PFC regions to the evaluation of alternate strategies, nor can they exclude the potential contribution of the lateral PFC and other PFC regions to the evaluation of the selected strategy. These uncertainties may stem from the complicated properties of the brain including functional heterogeneity and balanced excitation and inhibition (E/I), in addition to the limited spatial and temporal resolutions of fMRI, and the univariate nature of GLM-BA.

Functional heterogeneity refers to the findings that neurons within any cortical region including the primary sensory cortex are highly heterogeneous in functional activities (Horton and Adams, 2005; Isaacson and Scanziani, 2011; Swindale, 1998). For example, the primary visual cortex is structurally and functionally organized to include overlapping maps, each responsive to a unique visual property such as edge orientation, motion direction, and spatial frequency. These overlapping maps form a so-called ‘polymap’ (Horton and Adams, 2005; Swindale, 1998). Likewise, it has been suggested that different functional networks (FNs) overlap with each other in the PFC (Fuster, 2009). Intermixed neurons in the same PFC regions show different timecourses including concurrent increases and decreases in activity during the delay period of a working memory task (Fuster, 2009). Relevant to the findings presented in the Donoso et al manuscript, fMRI studies have reported that the same regions in the medial and lateral PFC show relatively increased BOLD signals during multiple tasks of different cognitive demands, including working memory, task novelty, and response conflict (Duncan and Owen, 2000). It has been suggested that these medial and lateral PFC regions form a multiple-demand system (Duncan, 2010).

Balanced E/I refers to the findings that excitatory and inhibitory activities are accompanied with each other among adjacent cortical neurons during either resting condition or task performance (Isaacson and Scanziani, 2011). Within any cortical region, about 20% of all neurons are GABAergic inhibitory interneurons and 80% are excitatory pyramidal neurons (Druga, 2009). These inhibitory and excitatory neurons form dense connections and maintain a balance of E/I at levels of single neurons and microcircuits. Spontaneous or stimulus-induced activation of cortical neurons is accompanied by deactivation of adjacent neurons with different functional properties, although the ratio between activation and deactivation may change dynamically (Isaacson and Scanziani, 2011). A typical fMRI voxel in the cortex contains more than one million neurons (Logothetis, 2008). The property of balanced E/I predicts that within each voxel at any instant, task-related neuronal activation is accompanied by simultaneously deactivation of adjacent neurons. Therefore, concurrent activation and deactivation of neurons should exist in both the medial and lateral PFC during each condition of the task used in the Donoso et al manuscript.

Although the exact coupling between neural activity and BOLD signal is not yet clear, there is consistent evidence from multiple studies indicating that activation increases BOLD signal while deactivation reduces BOLD signal (Goense et al., 2012; Logothetis, 2008; Mullinger et al., 2014). Therefore, BOLD signal changes from each voxel probably reflect the changes in difference between activation and deactivation of all neurons in the voxel, not activation or deactivation alone (Logothetis, 2008). Increases in BOLD signal probably reflect a greater activation then deactivation, while decreases in BOLD signal reflect a greater deactivation than activation, and no change in BOLD signal may reflect cancellation of activation and deactivation among different neurons in the voxel, and does not necessarily indicate no activation. Since GLM-BA is a univariate analysis, it treats BOLD signal from each voxel independently and cannot reveal concurrent activation and deactivation of different neurons underlying BOLD signal changes from each voxel. Therefore, either no significant change or a significant decrease in BOLD signal at any cortical region as revealed by GLMBA does not necessary prove there is no significant neuronal activation in the region. Since the Donoso et al manuscript (Donoso et al., 2014) used a GLM-BA alone, they cannot rule out task-related activation in any brain regions during evaluation of the reliability of selected or alternate response strategies, regardless of whether these brain regions show no change or significant decreases in BOLD signal during task performance.

The above views have received direct support from recent fMRI studies using sICA (Beldzik et al., 2013; Geranmayeh et al., 2014; Xu et al., 2014; Xu et al., 2013b). In fMRI, sICA assumes BOLD signal from each voxel represents a linear mixture of source signals and separates this signal mixture into spatially independent components (i.e., source signals), which represent temporally coherent functional networks (FNs) (Calhoun and Adali, 2012). One study used both a GLM-BA and sICA to assess task-related changes in BOLD signal while a group of healthy participants performed a visual task with parametric demands of attention and working memory (Xu et al., 2013b). The GLM-BA revealed load-dependent increases in BOLD signal in the intra-parietal sulcus, dorsolateral PFC, and insula, bilaterally, and decreases in BOLD signal in the medial frontal and parietal cortex. In contrast, sICA found that FNs showing load-dependent positive and negative modulations in timecourses occupied much more extensive brain regions than those that showed positive

and negative changes in BOLD signal, respectively, as revealed by the GLM-BA. Furthermore, positive and negative FNs overlapped extensively with each other. Some positive FNs overlapped with brain regions showing decreases in BOLD signal as revealed by the GLM-BA, while some negative FNs overlapped with brain regions showing increases in BOLD signal. These findings from sICA indicate that each voxel within FN overlap regions contains multiple source signals of different timecourses. These source signals may show task-related concurrent increases and decreases. Therefore, these findings of sICA: are highly consistent with the above-predicted concurrent activation and deactivation of different neurons in a voxel based on balanced E/I; support our view that no change or significant decreases in BOLD signal does not necessarily imply no activation; and indicate that the sensitivity and specificity of GLM-BA are limited.

The limitation of GLM-BA has been discussed previously for reasons that GLM-BA is a model-driven approach based on explicitly defined hypotheses and hemodynamic response functions (HRFs) which may not capture variable features of HRFs in different brain regions (Hu et al., 2005; McKeown, 2000; McKeown et al., 1998). Therefore, some investigators have proposed to use both GLM-BA and ICA to reveal more task-related brain activity than using GLM-BA alone (Calhoun et al., 2005; Hu et al., 2005; McKeown, 2000). Here, based on the brain properties of functional heterogeneity and balanced E/I, we further emphasize the importance of using sICA (or some other approach which can account for overlap cancelation) in conjunction with GLM-BA in future fMRI studies for a more complete understanding of brain functional organization (Xu et al., 2013a).

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Reference

1. Beldzik E, Domagalik A, Daselaar S, Fafrowicz M, Froncisz W, Oginska H, Marek T. Contributive sources analysis: a measure of neural networks' contribution to brain activations. Neuroimage. 2013; 76:304–312. [PubMed: 23523811]
2. Calhoun VD, Adali T. Multisubject independent component analysis of fMRI: a decade of intrinsic networks, default mode, and neurodiagnostic discovery. IEEE Rev Biomed Eng. 2012; 5:60–73. [PubMed: 23231989]
3. Calhoun VD, Adali T, Stevens MC, Kiehl KA, Pekar JJ. Semi-blind ICA of fMRI: A method for utilizing hypothesis-derived time courses in a spatial ICA analysis. Neuroimage. 2005; 25:527–538. [PubMed: 15784432]
4. Donoso M, Collins AG, Koechlin E. Human cognition. Foundations of human reasoning in the prefrontal cortex. Science. 2014; 344:1481–1486. [PubMed: 24876345]
5. Druga R. Neocortical inhibitory system. Folia biologica. 2009; 55:201–217. [PubMed: 20163769]
6. Duncan J. The multiple-demand (MD) system of the primate brain: mental programs for intelligent behaviour. Trends Cogn Sci. 2010; 14:172–179. [PubMed: 20171926]
7. Duncan J, Owen AM. Common regions of the human frontal lobe recruited by diverse cognitive demands. Trends in Neurosciences. 2000; 23:475. [PubMed: 11006464]
8. Fuster JM. Cortex and memory: emergence of a new paradigm. J Cogn Neurosci. 2009; 21:2047–2072. [PubMed: 19485699]

9. Geranmayeh F, Wise RJ, Mehta A, Leech R. Overlapping Networks Engaged during Spoken Language Production and Its Cognitive Control. J Neurosci. 2014; 34:8728–8740. [PubMed: 24966373]
10. Goense J, Merkle H, Logothetis NK. High-resolution fMRI reveals laminar differences in neurovascular coupling between positive and negative BOLD responses. Neuron. 2012; 76:629–639. [PubMed: 23141073]
11. Horton JC, Adams DL. The cortical column: a structure without a function. Philos Trans R Soc Lond B Biol Sci. 2005; 360:837–862. [PubMed: 15937015]
12. Hu D, Yan L, Liu Y, Zhou Z, Friston KJ, Tan C, Wu D. Unified SPM-ICA for fMRI analysis. Neuroimage. 2005; 25:746–755. [PubMed: 15808976]
13. Isaacson JS, Scanziani M. How inhibition shapes cortical activity. Neuron. 2011; 72:231–243. [PubMed: 22017986]
14. Logothetis NK. What we can do and what we cannot do with fMRI. Nature. 2008; 453:869–878. [PubMed: 18548064]
15. McKeown MJ. Detection of consistently task-related activations in fMRI data with hybrid independent component analysis. Neuroimage. 2000; 11:24–35. [PubMed: 10686114]
16. McKeown MJ, Makeig S, Brown GG, Jung TP, Kindermann SS, Bell AJ, Sejnowski TJ. Analysis of fMRI data by blind separation into independent spatial components. Hum Brain Mapp. 1998; 6:160–188. [PubMed: 9673671]
17. Mullinger KJ, Mayhew SD, Bagshaw AP, Bowtell R, Francis ST. Evidence that the negative BOLD response is neuronal in origin: A simultaneous EEG-BOLD-CBF study in humans. Neuroimage. 2014; 94C:263–274. [PubMed: 24632092]
18. Swindale NV. Cortical organization: modules, polymaps and mosaics. Curr Biol. 1998; 8:R270–R273. [PubMed: 9550692]
19. Xu J, Calhoun VD, Pearlson GD, Potenza MN. Opposite Modulation of Brain Functional Networks Implicated at Low vs. High Demand of Attention and Working Memory. PLoS One. 2014; 9:e87078. [PubMed: 24498021]
20. Xu J, Potenza MN, Calhoun VD. Spatial ICA reveals functional activity hidden from traditional fMRI GLM-based analyses. Frontiers in neuroscience. 2013a; 7:154. [PubMed: 23986654]
21. Xu J, Zhang S, Calhoun VD, Monterosso J, Li CS, Worhunsky PD, Stevens M, Pearlson GD, Potenza MN. Task-related concurrent but opposite modulations of overlapping functional networks as revealed by spatial ICA. Neuroimage. 2013b; 79:62–71. [PubMed: 23611864]

Highlights

- Cortex is functional heterogeneous and maintains balanced excitation and inhibition.
- Opposite changes in activity among adjacent neurons may cancel their effects on fMRI signal.
- No or negative fMRI signal changes during any task do not mean no task-related neuron activation.
- Spatial ICA may reveal more task-related brain activity than GLM based analysis alone.