Deactivations, Global Signal, and the Default Mode of Brain Function

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The concept of deactivation in functional MRI (fMRI) has recently gained greater acceptance as a physiological process rather than an artifact of image analyses or shunting of blood flow. It is likely that recent studies demonstrating decreases in the rate of oxygen metabolism (Shmuel, Yacoub, et al., 2002) and local field potentials (Shmuel, Augath, et al., 2003) in regions of deactivation have contributed to this greater acceptance. However, the signal change in fMRI is relative, and the concept of a deactivation suggests that there is some state that can be used as a standard baseline (Newman, Twieg, & Carpenter, 2001; Raichle et al., 2001; Stark & Squire, 2001). Deactivations are BOLD signal decreases that occur during a task relative to this standard baseline. Several recent studies have identified specific brain regions (inferior parietal, posterior cingulate, medial temporal/parahippocampal, and medial prefrontal cortices) that are active while subjects rest quietly and are deactivated during attention-demanding tasks (McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003; Gusnard & Raichle, 2001; Raichle et al., 2001; Binder et al., 1999). The article published in this issue of the *Journal of Cognitive Neuroscience* by Michael D. Greicius and Vinod Menon (Default-Mode Activity during a Passive Sensory Task: Uncoupled from Deactivation but Impacting Activation) uses independent component analyses (ICA) to investigate this ''default mode'' of brain function in a dataset from the fMRI Data Center archive (Laurienti et al., 2002). The primary hypothesis presented in the manuscript is that the default-mode network will not be deactivated during passive stimulation. This hypothesis is based on the idea that passive sensory stimulation does not demand attentional resources and will not suppress activity in this network. The investigators suggest that it will be possible to identify the default-mode network even in the absence of stimulus-induced deactivation using ICA. The data clearly demonstrate that the analysis methodology is able to identify a predefined network of brain regions providing further evidence that there is, in fact, a default-mode brain network.

In addition to the main findings, this study again raises the important issue of global normalization that often surrounds studies evaluating deactivations (Macey, Macey, Kumar, & Harper, 2004; Gavrilescu et al., 2002; Desjardins, Kiehl, & Liddle, 2001; Aguirre, Zarahn, & D'Esposito, 1998). The process of global normalization is designed to remove whole-brain signal changes that can act as confounds in studies designed to evaluate regional signal changes (Aguirre et al., 1998). There have been several methods developed to remove unwanted global signal changes (Macey et al., 2004; Gavrilescu et al., 2002; Andersson, Ashburner, & Friston, 2001; Desjardins et al., 2001; Andersson, 1997). If the global signal is correlated with the time course of the stimulation paradigm, artifacts can occur when commonly used normalization procedures, such as proportional scaling, are used. Specifically, if the global signal is positively correlated with the stimulus time course, the global normalization procedure can induce extensive regions of artifactual deactivations (Gavrilescu et al., 2002; Desjardins et al., 2001; Aguirre et al., 1998) and can include white matter, as noted by Greicius and Menon in their article. It is important to recognize that although the global normalization procedure can induce artifacts in the results, the global signal change that is correlated with the paradigm may not be an artifact itself.

It has been reasoned that global signal changes can be an ''artifact'' when the whole-brain mean signal increases due to large regional signal increases (Aguirre et al., 1998). Such large ''regional'' increases in signal can elevate the ''global'' signal even if increases were localized to the activated brain areas. In such a case, the global normalization procedure will artificially decrease the signal (artifactual deactivations) in regions that exhibit no correlation with the stimulation paradigm, including the white matter. However, it is also possible that there are true global signal changes where the total brain blood flow changes in concert with the stimulation paradigm. In fact, it has been shown that the global cerebral blood flow (CBF) can actually decrease during painful stimulation (Coghill, Sang, Berman, Bennett, & Iadarola, 1998. This finding of global CBF decreases in the presence of significant activity increases suggests that large regional areas of activity may not account for the global signal change in all studies. It is interesting to note that when global signal is negatively correlated with the stimulation time course, the global normalization

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procedure can induce artifactual activations (including white matter areas).

A recurrent finding in the studies evaluating global signal changes is that global normalization procedures produce signal changes in the white matter and in the cerebrospinal fluid, where little or no BOLD signal changes should occur, naturally leading to the conclusion of Greicius and Menon that the observed changes are artifacts. This finding of white matter and CSF deactivation suggests that there may be tissue-specific factors resulting in the observed artifacts. In fact, many normalization procedures assume that the global signal change is distributed across all regions with no spatial variation in magnitude (Macey et al., 2004). This assumption may be the source of much of the deactivation artifacts observed with normalization procedures.

CBF in the gray matter (65.3 mL/100 g tissue/min) is more than three times the value of blood flow in the white matter (21.4 mL/100 g tissue/min) as measured by positron emission tomography (Frackowiak, Lenzi, Jones, & Heather, 1980). This difference in perfusion between the two tissue types is maintained following acetazolamide-induced increases (Yen et al., 2002) and caffeine-induced decreases (Field, Laurenti, Yen, Burdette, & Moody, 2003) in CBF. Thus, when blood flow to the brain increases by some percentage of steady state, the amount of increase in any particular brain region is proportional to the baseline flow in that area. If the global flow increases during a stimulation paradigm, the gray matter will experience a larger absolute increase than the white matter. The use of global normalization procedures that assume spatial uniformity of the global signal will result in artifactual deactivations in areas that exhibited smaller absolute changes (white matter and CSF). Quite importantly, however, it is unlikely that deactivations identified in the gray matter following global normalization are the consequence of such an artifact. A recently proposed method for the removal of global signal changes that allows spatial variation in the magnitude of the signal (voxel-level linear model of the global signal) can be used to account for blood flow differences in multiple tissue types (Macey et al., 2004).

The challenges associated with removing global signal changes that are correlated with the stimulation paradigm remain problematic even with the newer methodologies (Macey et al., 2004). It has been suggested that normalization of each tissue type independently could avoid problems associated with stimulus-correlated global signal changes. However, such methodologies are extremely time consuming and are not widely used. A common method used to deal with task-correlated global signal changes is to simply eliminate global normalization from the analysis (Greicius & Menon, 2004; Aguirre et al., 1998). Unfortunately, regional signal decreases that are negatively correlated with the paradigm design (true deactivations) can be masked by correlated global signal increases. This raises the distinct possibility that brain regions accurately exhibiting signal decreases during a task will not be identified if global normalization is omitted, leading to a potential spurious interpretation of the deactivation results. The growing evidence that there is a network of brain areas active at rest and deactivated by demanding tasks suggests that deactivations may be critical for our understanding of brain function. In addition, evidence for cross-modal deactivations in the sensory cortices is also growing (Beauchamp, Lee, Argall, & Martin, 2004; Crottaz-Herbette, Anagnoson, & Menon, 2004; Wright, Pelphrey, Allison, McKeown, & Mc Carthy, 2003; Laurienti et al., 2002; Macaluso, Frith, & Driver, 2000; Kawashima, O'Sullivan, & Roland, 1995; Haxby et al., 1994), suggesting that certain tasks turn on and turn off ''specific'' regions of the cortex.

The manuscript by Greicius and Menon provides further important evidence that there is a default-mode network that is active in the absence of attention-demanding tasks. The ICA was able to identify these brain regions even in the absence of deactivation and in a dataset that exhibited artifacts in the white matter associated with global normalization. It would be very interesting to evaluate the use of ICA as a tool for global normalization in datasets with global signal changes that are correlated with the stimulation paradigm. The results also demonstrate the utility of a brain imaging database and emphasize that different analysis methods may be used to address different questions even in the same dataset.

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