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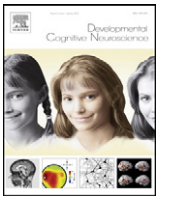

Comment

Comment on "The physiology of developmental changes in BOLD functional imaging signals" by Harris, Reynell, and Attwell

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Accurate measurement of the variable of interest is critical to successful science. Hemodynamic measurements of the blood oxygen level dependent (BOLD) fMRI signal are continually improving in human fMRI studies. As we progress, it is imperative to re-examine previous assumptions as measurement techniques advance and as more information about lurking variables is learned.

Harris, Reynell, and Attwell, in a Developmental Cognitive Neuroscience article published earlier this year, raise several concerns when comparing children and adults using fMRI BOLD data. They do so in the context of discussing numerous potential age-related changes in neurovascular coupling, neural circuitry, and neural energy use that have not been widely explored thus far in the developmental fMRI literature (Harris et al., 2011). Considering these potential issues, the authors express concern about the feasibility of comparing children and adults using fMRI.

We, and others, have previously discussed many important elements of study design, analysis, and interpretation in developmental imaging (e.g. Palmer et al., 2004; Church et al., 2010; Poldrack, 2010; Luna et al., 2010; Carp et al., 2011). The considerations raised in these discussions, and in the piece by Harris et al., are targeted at developmental imaging but really are germane to studies across the lifespan and to studies that compare groups (e.g. patients and controls).

In their detailed and thoughtful discussion, Harris, Reynell, and Attwell focus specifically on what these potential underlying structural and vascular differences could mean to results of BOLD signal *differences* found between children and adults. This focus on accounting for differences is understandable as it is differences that are primarily highlighted in developmental (and aging) studies. Thus, it is paramount to question the underlying properties of the images that could lead to confounding differences.

Importantly, both in our own experience performing developmental studies, and in all developmental studies with which we are familiar, (1) adult and child % signal change of BOLD activity is not significantly different for the vast majority of the brain, and (2) when differences are observed, they are task specific, not task general. These points, we posit, are substantial evidence against wholesale problems over development with differential neurovascular coupling.

Let us consider the former observation, that, for the most part, the brains of adults and children look very similar while performing most tasks. While a number of reasons exist why a given difference could be due to a lurking variable (such as differences in neurovascular coupling), it is difficult for broad, pervasive similarities to be accounted for in the same argument. The observation across developmental studies that the level of activity in only a minority of regions is different over age, and that the particular regions vary by task substantially mitigates the concerns raised by Harris et al.

For example, we find regions of difference between children and adults in tasks requiring subjects to read or repeat single words (Church et al., 2008), but also find that the majority of the brain regions active during either task are not different between the groups. We also find clear differences due to stimulus modality (i.e. auditory versus visual) in auditory and visual cortex that are not different by age. These results suggest, but do not prove, the existence of a similar underlying parenchyma that allows consistent reactions to external stimuli over age.

The second observation, that differences observed over age are largely task-specific and not task-general, is discussed in more detail in Church et al., 2010. In that article, we posited that, given much of the brain's activity for a particular task is the same over the ages typically studied, if different tasks can produce opposing patterns of activity for 2 age groups within the same region, the difference is unlikely to be due to vascular differences.

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Harris, et al. comment on this position stating that the argument, though reasonable, is not sufficient, because different inputs to a given area could have different vascular relationships to neuronal activity, and these relationships could change over age. Though this potential neurovascular coupling-mediated mechanism is quite complex, and would be difficult to reconcile with the fact that, for the most part, children and adults have similar activation patterns and magnitudes, we take their point that it is possible. Ruling in or out such a mechanism is presently beyond the reach of human fMRI research.

Given the current inability, due to the macro-level nature of fMRI techniques, to address directly in humans many of the issues discussed in their article, Harris et al. present 3 recommendations for moving forward. First, they recommend awareness of these issues (e.g. neurovascular coupling) and how they may affect a given region of interest to allow for more accurate interpretation of results. Second, when that information is not available, study designs that allow investigation of the same region in many different conditions could allow leverage for teasing apart substrate or vascular differences from task-related differences. Third, they suggest documenting BOLD changes over development in simpler "low level" circuits such as sensory cortex. We heartily agree with all of their recommendations, and in fact have taken steps towards all of these suggestions in our own work.

Relevant to the first and second points, the BOLD timecourse shapes throughout the brain may be influenced by different vascular couplings. By not using an assumed response shape in our analyses, we allow the possibility for these inter-regional differences to occur and be observed, as well as to vary potentially between groups (though we have neither systematically examined nor qualitatively observed BOLD timecourse shape differences over age). Apropos of the third suggestion, in Kang et al. (2003) and Wenger et al. (2004) we examined the BOLD signal in visual and motor cortex using different fMRI experimental designs (event-related and mixed block/event-related) using precisely the type of stimuli and task paradigm that Harris et al. suggest (e.g. flickering checkerboards and button-press responses). These investigations characterized the BOLD response in 7–8 years olds and compared the response to that in young adults. Both studies have shown that the BOLD signal is not substantially different between school-age children and young adults in the motor or visual cortex using this paradigm, suggestive that potential age differences in the neuronal substrate are at least not affecting primary sensory and motor cortex in a way that is statistically reliable. While visual and motor cortex and their neurovascular relationships may be expected to be fairly mature by that time, the purpose in comparing those ages was a pragmatic one. We were investigating the development of controlled lexical processing from age 7 years onward, and we wanted to make sure that age-related differences in neurovascular calibration were not masquerading as age- or performance-related functional neuroanatomical differences (Schlaggar et al., 2002; Brown et al., 2005). We are unaware of such an investigation in younger children and agree with Harris et al. that such studies would be meritorious.

Another important method that developmental cognitive neuroscientists can use to lessen the chance of being swayed by lurking variables is to bring many different types of data to bear on the problem of interest. Anatomical information is collected for each subject as part of the scanning process, and thus group anatomical differences could be explored and potentially be included to contextualize functional findings. Similarly, more groups are collecting DTI and/or resting-state fMRI data as part of a scanning session, and these data also can prove useful for framing functional results. Overall, using conservative, multiple comparison-corrected statistics in our developmental comparisons to avoid misattributions, by looking across studies of development for consistencies and inconsistencies, and interpreting results in the context of extant functional, structural, lesion, and animal studies, we will learn more in the future about whether potential neurovascular differences are contributing to developmental fMRI results.

Harris et al. provide an important article that thoroughly considers issues related to the BOLD signal generation in a developmental context. The article calls into question prior assumptions, an endeavor we believe to be highly valuable. We concur that when interpreting group differences it is important to keep in mind that, however well matched, there are many potential lurking variables at play in the developing and mature brain. However, we contend that while neurovascular coupling differences cannot be taken off the table as a concern, the weight of the concern is mitigated by several lines of evidence.

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