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Comments and Controversies

The blind, the lame, and the poor signals of brain function—A Comment on Sirotin and Das (2009)

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ABSTRACT

Last year, a study appeared that questioned the generally held assumption of a generic coupling between electrical and hemodynamic signs of neural activity (Sirotin and Das, 2009). Although the findings of that study can barely surprise the specialists in the field, it has caused a considerable confusion in the nonspecialist community due to the unwarranted claim of having discovered a "hitherto unknown signal." According to this claim, functional magnetic resonance imaging (fMRI) would pick up not only signals that reflect electrical brain activity but also purely hemodynamic signals that are not linked to neural activity. Here, we show that that study's failure to obtain significant electrophysiological responses to task structure is easily understood on the basis of findings reported for related functional paradigms. Ironically and counter its intention, the study by Sirotin and Das reminds us of the exquisite sensitivity of spatially pooled hemodynamic signals and the limitations of recording only very local samples of electrical activity by microelectrodes. We suggest that this sensitivity of hemodynamic signals should be converted into spatial resolution. In other words, hemodynamic signals should be used to create maps. Further, we suggest that electrical recordings should be obtained at systematically varying functional positions across these maps. And we speculate that under such appropriate experimental and analytical circumstances correspondence between the two modalities would be retrieved—at the expense of a novel signal lost in oblivion.

The advent of fMRI has had a major impact on the neurosciences and in particular on studies of cognitive function. It exploits a signal-blood-oxygenation-level-dependent (BOLD) contrast—that is indirect and blurred both spatially and temporally with respect to electrical neural activity. The mechanisms of neurovascular coupling are still not fully understood but landmark studies have provided a fairly detailed description of how features of electrical neural activity translate into fMRI signal in a generic and reproducible way (Logothetis et al., 2001; Thompson et al., 2003; Niessing et al., 2005; Shmuel et al., 2006). One recent study challenges this relationship and is thus of interest to the entire functional neuroimaging community (Sirotin and Das, 2009). Yet, the actual findings of that experiment merit closer consideration and do not support this claim.

Imagine you were one of the two monkeys in this recently conducted study. You were taught by training that your juice reward depends on maintaining fixation during an equiluminant color change in "one single star in an otherwise black night sky." Obviously, you will need to pay a lot of attention to the target to do the job but, unfortunately, occasional strong visual stimuli will occur in your visual field at roughly 2° distance from the target point. Faced with this functional challenge, an optimized neuro-behavioral strategy will consist in making your visual cortex specifically sensitive to stimuli at your point of fixation, that tiny star, and insensitive to the threat posed by the supernovas exploding close by. Fortunately, you are warned each time this might happen because such distracting stimuli will appear only 2 s after the onset of a trial requiring your fixation.

What is the spatiotemporal pattern of brain activity modulations in response to these demands and how does it relate to performance? Similar situations as the one described above have been investigated in behavioral experiments and more recently also in functional neuroimaging studies. The latter have shown that as early as in primary visual cortex spatial and temporal cueing of attention induces preparatory activity changes with enhanced resources made available in advance to those parts of cortex representing the focus of attention (Somers et al., 1999; Brefczynski and DeYoe, 1999; Müller et al., 2003).

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But what about the representation of the remaining unattended and potentially distracting visual field that was covered in the study by Sirotin and Das?

One of the first neuroimaging studies speaking to this issue was conducted in nonhuman primates (Vanduffel et al., 2000). Using a double-label technique of glucose uptake as an index of neural activity, Vanduffel and colleagues compared metabolic activity in the early visual system under two different paradigms with closely matched visual stimulation. In one case, monkeys had to perform a difficult perceptual task at their point of fixation, in another detect a target in the periphery of the visual field, once they had a received a central cue. In other words, in the latter case visual input remote from the fixation point was task-relevant, in the former it was not. These different functional demands yielded a relative suppression of metabolic activity in the representation of the peripheral visual field whenever the task had to be performed on visual input at the fixated location and sensory input in the periphery was thus potentially distracting. Metabolic activity at the representation of the fixated location was enhanced compared to the condition where the target appeared in the periphery. The spatial extent of this central enhancement scaled with the size of the task-relevant stimulus. In other words, this metabolic response pattern was tightly tuned to specific task demands. Interestingly, for the smallest size of task stimuli used by Vanduffel et al., the zero crossing of the metabolic effect was at about 1° to 2° distance from the representation of the fixation spot.

Most studies in human subjects have used paradigms involving covert spatial attention shifts where central gaze fixation is maintained but the allocation of attention is cued to a peripheral location. Such studies have extended the findings in monkeys by showing that central cueing of attention to peripheral locations is in itself sufficient to increase activity levels in cortex representing those peripheral locations (Somers et al., 1999; Brefczynski and DeYoe, 1999; Kastner et al., 1999; Müller et al., 2003). And neuroimaging studies have also established that this correlate of the attentional "spotlight" is associated with decreased activity in cortex serving adjacent representations (Müller et al., 2004; Hopf et al., 2006). As this effect extends over hemifields and hence hemispheres, it is not due to any vascular "steal" epiphenomenon that might occur in the surround of activated tissue. The overall pattern of attention-induced preparatory signal change resembles a "Mexican hat" configuration, an antagonistic center-surround organization that is well-known from sensory physiology where this principle serves contrast enhancement.

More recently, we have studied the pattern of visual cortex activity under conditions of central fixation and characterized the effects of peripheral distracters as well as of a high load perceptual task, detecting a target embedded into a rapid serial visual stream (Heinemann et al., 2009). We found that similar as for attention allocated to peripheral locations, this setting was associated with enhanced activity in the representation of target locations and that this activity increase was surrounded by an extended zone of decreased activity, especially if the periphery contained distracting input (Fig. 1). As a function of task and distracters the zero crossing of this effect occurred for representations at approximately 1.5° distance from the point of fixation.

How do these findings relate to the report by Sirotin and Das? The published data show time courses for hemodynamic (recorded by optical imaging) and electrical signals (recorded by extracellular electrodes). Optical imaging was performed in a window covering V1 representations corresponding to visual field eccentricities ranging from about 1° to 5°. Signal time courses were averaged over the full area whereas electrodes naturally sample from a much more constrained volume surrounding the electrode tip. Maybe more critically, however, these sampling sites were eccentric with respect to the optical imaging window, clustering at about 2° off fixation, as specified in a table of the supplementary information (Sirotin and Das, 2009). We can conclude from this that modality-related signals from very different sizes of neural populations were compared. Averaged across the entire window, the hemodynamic time courses show a trial-related signal change that—assuming usual hemodynamic latencies—would be interpreted as a suppression of neural activity (with a brightening that indicates a blood volume reduction). As outlined above, this effect would be expected for unattended locations under the conditions of this paradigm. In other studies, this effect is fairly weak but widely distributed and therefore well captured by averaging over a wider range of cortex—and that of course associated changes in blood supplying vessels are at the source of this hemodynamic effect goes without saying. In light of the aforementioned spatial patterns of hemodynamic signal changes in related studies we can moreover conclude that sampling of electrical responses was not performed at a representative site but on the slope of the putative Mexican hat that we can assume to be centered on the central visual field representation. In other words, electrical records were obtained close to the likely zero crossing of the hemodynamic pattern. In the presence of neurovascular coupling, one would hence also expect the electrical effect at this location to be weak or absent. With this in mind, it comes as no surprise that the predictive power of electrical responses at these locations (essentially absent or variable) for hemodynamic responses across the optical imaging window was low. Following the logic outlined above, however, it would have been more sensible to test the predictive power of that signal which is consistently informative with respect to task structure, i.e., the hemodynamic response, for the electrical records and to then obtain such records at multiple different eccentricities from the central target. In the example of Fig. 2A of the Sirotin and Das publication, mere eyeballing of the lower right

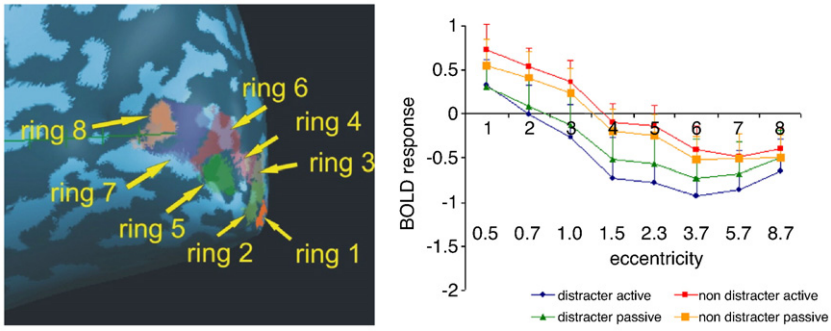

Fig. 1. Left: The coloured patches denote primary visual cortex representations of ring-shaped visual field regions with increasing eccentricity (ring 1: innermost ring, ring 8: outermost ring, representative data of one subject). Right: fMRI signal changes in the visual cortex representations of ring 1 to 8 during task completion (passive or active watching of a central letter stream presented either in an otherwise empty visual field or together with distracting peripheral letters). Activity was assessed in individually defined visual cortex representations and then averaged across subjects; inserted numbers indicate visual field eccentricity of each ring in degrees (adapted from Heinemann et al., 2009).

panel is nonetheless sufficient to detect a reduction of electrical activity across all frequency bands that is time-locked to the duration of an unstimulated "dark" trial and that is matched by a delayed hemodynamic signal modulation.

Instead of assuming neurovascular coupling and using what is known about spatial patterns of neural activity modulation during spatial attention, however, Sirotin and Das interpret their failure to detect an electrical response during anticipation as positive evidence of a "hitherto unknown signal." In the wake of this claim, more explicit accounts of which mechanisms could underpin purely vascular task-related signals have been proposed (Tan, 2009) but the question whether we actually need such an account has remained unanswered. Interpreting negative findings is of course a problem in itself but such claims are simply not tenable when signals are sampled from glaringly different neural populations and when the subsample studied in one modality cannot be considered representative of the larger sample studied in the other. Sirotin and Das apparently tried to make negative electrical findings during anticipation (of distraction) interpretable by contrasting them with positive evidence of electrical and hemodynamic responses that were obtained during visual stimulation at visual field sites corresponding to the electrode position. The deficiency of this reasoning for comparing negative and positive findings is that the positive findings are obtained by aligning a strong bottom-up signal to the electrical recording site. Hence, this situation simply restores or at least improves the matching between the two neural samples recorded in each modality and, not surprisingly, permits retrieving a good correlation across signals.

The data presented by Sirotin and Das illustrate that in cases of spatially patterned responses, local electrical signals sampled at inappropriate locations can be blind (or close to it) and it would be interesting to see where at corresponding locations hemodynamic responses turn blind as well. In other words, it would have been more informative if the authors of that study had used hemodynamic signals for what they are best at, mapping, as done in related studies (Shmuel and Grinvald, 1996; Devor et al., 2003; Sheth et al., 2004), rather than being collapsed across a large extent of cortical surface, presumably for sensitivity reasons.

The data also remind us that hemodynamic signals are lame, temporally dispersed to the point that it is difficult to functionally relate them to precise time points in the sequence of their paradigm. The authors themselves do not seem to fully master this lameness. For an experiment involving task-related hemodynamic signal modulations, the authors of the study remain remarkably coy about the use of standard terms as "activation" or "deactivation" to describe their findings. This may have to do with a lack of clear-cut predictions of what to expect in this functional setting but it may also reflect the well-known difficulties related to the use of a cyclic protocol with mostly short period lengths. Of note, the Fig. 2A of Sirotin and Das suggests that the peak of blood volume increase that signals "activation" is delayed by about 5 s with respect to the onset of visual stimulation (upper left panel). The same delay in "dark" trials shows a brightening that indicates reduced blood volume and hence "deactivation" (upper right panel). The relevant time point with respect to anticipation is somewhere between onset of the 4 s trial and 2 s later when potential distracting stimulation can be expected for the rest of the fixation trial, as indicated in left-sided panels of that figure. In the next figure, the authors then assign by a red arrowhead a brightening effect to a still ongoing trial without any delay. In other words, they are looking at an effect one trial too early. This makes them mistake the subsequent darkening, which would correspond to activation, for the effect that is associated with temporal trial structure. They erroneously conclude that the "trial-related signal is thus unlikely to be due to neuronal signals active only during the cued 'fixate' period." Yet, if one assumes appropriate hemodynamic delays and neuronal deactivation during the trial, the observations especially for transitions between short and long trials again come as no surprise.

There are several more such specialist issues that require attention in this study but fully detailing them would be beyond the scope of this comment. Briefly, for instance, in both "stimulated" and "dark" trials the deviations from the time course predicted by local electrical activity were prominent in time bins preceding those of visual stimulation, whether it occurred or not, but were highly variable. Such trial-by-trial variability in cued attention has also been shown in functional neuroimaging and translates directly into perceptual performance (e.g., Sapir et al., 2005) of which the study by Sirotin and Das, however, provided no direct measure. The use of normalization to pretrial baseline is especially disputable in such settings and seems to have impacted on power estimates in the most likely frequency band to follow task structure, the so-called alpha range of 8 to 12 Hz (see context-dependent prestimulus power differences in the lower panels of Fig. 2A).

To conclude, one may question whether the study by Sirotin and Das would not suggest to those neuroscientists who consider behavior as their ultimate explanandum, to use the lame hemodynamic signals and abandon the apparently blind electrophysiological signals. Dedicated psychophysical studies have now established the behavioral significance of the hemodynamic Mexican hat pattern of visual cortex activity under conditions of focused attention (Cepeda et al., 1998; Mounts, 2000; Cutzu and Tsotsos, 2003; Müller et al., 2005; Sylvester et al., 2008). From these studies, we also know that our capacity to inhibit neighboring distracters has limitations which presumably reflect receptive field sizes in task-relevant visual cortex. In the study of Sirotin and Das, only the hemodynamic signal provided a putative neural correlate of anticipatory attention. That this signal correlated with trial onsets and not with reward only underlines this interpretation because the occurrence of reward (and not its timing) was dependent on fixation during the trial and thus potentially jeopardized by distracting input.

What the study by Sirotin and Das hence also reminds us of is that any signal can be a poor signal if wrongly studied in an application to neuroscientific questions. Its tacit assumption—that very locally sampled electrical activity provides a gold standard to understand brain processes—is simply the wrong starting point. Imagine the published outcome of an experiment which had found a task effect in local electrical but not in macroscopically analyzed hemodynamic signals. Readers of such a report would rightfully conclude that the latter is simply an insensitive or poor signal. The findings by Sirotin and Das (2009) show the opposite but the conclusion should be analogous. Why expect that a poor signal should have any predictive power for an informative signal, as hemodynamic responses are in this instance? Unfortunately, brain research has no single gold standard method and can only try to exploit the blessing of multimodal pluralism where each method has its own specific strengths but also drawbacks. To do so, requires optimizing the measurement and analysis of each signal but also remaining aware of inherent limitations when comparing results from different modalities. For both signals, however, the study by Sirotin and Das misses out on the important issue of where effects occur. In the case of hemodynamic signals, this is due to averaging across the window, and in the case of electrical signals to the sampling from in essence a single functional location (in terms of visual field position). As it stands, the findings by Sirotin and Das cannot in themselves be interpreted with confidence and should therefore not give rise to the conclusions they propose. It is certainly wise to retain reservations regarding the generality of neurovascular coupling and some spatiotemporal dissociations have indeed been reported across several scales (Thompson et al., 2003, 2005; Devor et al., 2008; Maier et al., 2008). But better evidence than that presented by Sirotin and Das is required before making substantial claims about novel signals and mechanisms. Such evidence could come from applying conjointly more directly comparable sampling techniques for electrical, metabolic and hemodynamic brain activity.

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