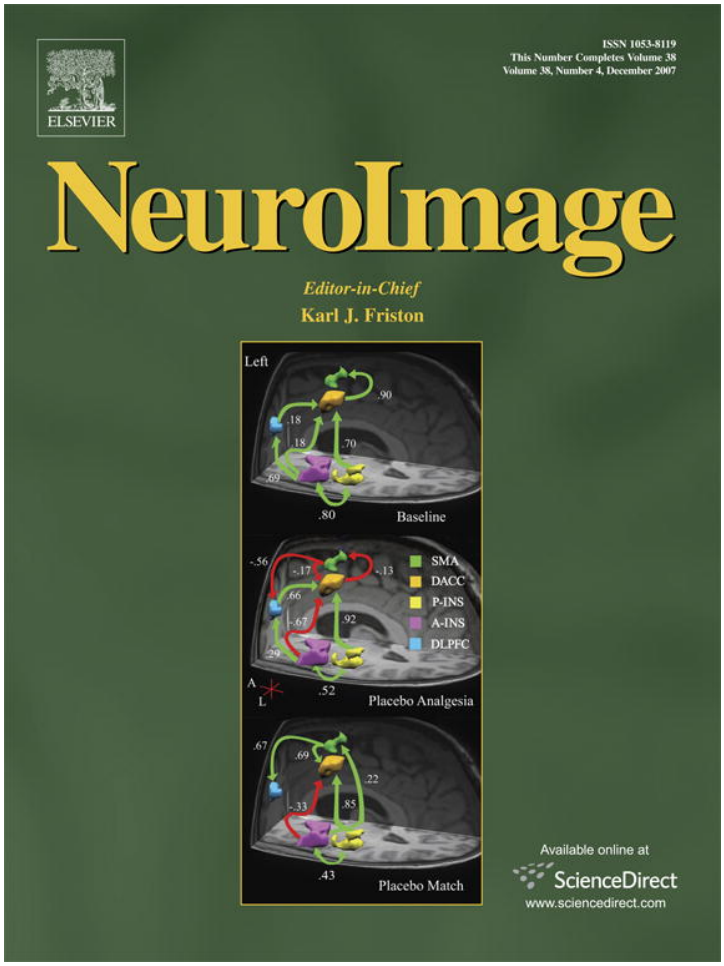

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Comments and Controversies

Different analysis solutions for different spatial resolutions? Moving towards a mesoscopic mapping of functional architecture in the human brain

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This comment challenges the dichtotomy that Kriegeskorte and Bandettini (this issue) propose to exist between "activation-based" and "information-based" approaches to fMRI analyses and argues that multi-variate analyses are just a special case within the overall repertoire of methods for analyzing paradigm-related BOLD signal variations. Moreover, this comment argues that using multi-variate approaches comes at a price, trading-off spatial resolution for sensitivity, and thus partially cancels potential benefits from high-field fMRI. Paradoxically, this comment thus concludes that pattern analyses provide a powerful complement to existing methods but not the complement that will actually permit to map functional architecture at mesoscopic resolution, i.e., one of the most interesting applications of high-field fMRI.

In their contribution to this issue of NeuroImage, Kriegeskorte and Bandettini (2007) state that four challenges result from the use of increasingly higher resolution for functional magnetic resonance imaging of human brain processes. Briefly, these challenges are related to lack of spatial precision in neurovascular coupling, sensitivity limitations of the signal, sensitivity limitations in uni-variate statistical analysis of multiple observations, and structural as well as functional inter-subject variability. Kriegeskorte and Bandettini suggest that "activation-based" analytical approaches will heavily suffer from, if not fail due to these challenges whereas "information-based" approaches will permit to overcome them. All individual challenges stated with respect to high-resolution fMRI are undoubtedly true, and it also appears likely that "information-based" approaches will provide valuable new insights into brain function. However, the actual logical link between these two aspects is far less compelling. Despite a promising start information-based approaches still await critical future tests to clarify their potential for advancing the neurosciences.

Regarding the aforementioned four challenges from high-field MRI, it is important to realize that all of these issues were already raised with the advent of fMRI, at the time expressed in relation to positron emission tomography. And they have been dealt with-overall quite successfully one might add. Paradoxically, one might even argue that since the earliest days of fMRI, high-resolution data acquisition has in fact been one of several proposed avenues for solving these challenges instead of aggravating them. The so-called brain-vein debate emerged within a year after the scientific community realized there was a new powerful tool for human brain mapping. This debate was fuelled by those studies that had shown early on the feasibility of high-resolution fMRI and thus directly visualized macroscopic veins as sources of strong effects (Frahm et al., 1993). In addition to other strategies, however, it was also proposed that effects in macroscopic veins vs. microscopic vessels in tissue might simply be differentiated by sufficiently high spatial resolution (e.g., Frahm et al., 1994).

Regarding sensitivity, the advent of high-field fMRI should logically help high-resolution fMRI by yielding comparable signal-to-noise ratios at much smaller voxel sizes than those feasible at lower field strength (Yacoub et al., 2001). Regarding statistical sensitivity, the current predominance of whole-brain fMRI reflects both the exploratory ambitions of the paradigms used by the community and the limited usefulness of dense temporal sampling of a signal that is smooth in time. Yet, since the early high-resolution fMRI studies (e.g., Kleinschmidt et al., 1994) and in particular with the advent of high-field fMRI (e.g., Pfeuffer et al., 2002; Shmuel et al., in press), many investigators choose to sacrifice volume coverage for smaller voxel size, thus inadvertently attenuating a whole-brain multiple comparisons problem, at the expense of restricting their conclusions to the tissue covered. Finally, high-resolution fMRI is the obvious way to map functionally defined areas subject-by-subject instead of

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relying on normalized stereotactic coordinates or structural anatomical landmarks.

It may therefore help to rephrase the dichotomy that Kriegeskorte and Bandettini (2007) introduce between "activation-based" and "information-based" analytical approaches. Both approaches rely on the same fMRI signal, BOLD contrast, and on its variations in relation to experimental conditions, commonly referred to as "activation" (or "deactivation"). Where they differ, is in whether they consider the "information" from the experimentally induced fMRI signal change independently voxel-by-voxel (spatially univariate), or whether they take an entire pattern across multiple voxels into account (spatially multi-variate, see for instance Cox and Savoy, 2003). In analyzing the performance of uni-variate approaches, however, Kriegeskorte and Bandettini (2007) tap into yet another and rather popular third class of approaches which spatially smooth signals or even average them across voxels contained in a region-of-interest (ROI).

Again paradoxically, and as stated by Kriegeskorte and Bandettini, this third class of analyses using ROIs has thrived in response to the four challenges outlined above. Regions of interest have been popular because fine-grained spatial analysis was felt to be beyond the reach of the BOLD signal, because sensitivity was boosted by averaging, because localizer-driven approaches circumvent in a hypothesis-driven way multiple comparisons and because ROI localization can be functionally defined on a subject-by-subject basis despite inter-individual variability (see Saxe et al., 2006). Similar considerations but also-and particularly at high field-additional considerations (Triantafyllou et al., 2006) apply to the use of smoothing kernels in voxel-by-voxel analyses but it is important to realize that smoothing is an optional and not an inevitable ingredient in uni-variate analyses and that its usefulness stands and falls with the specific issue under investigation.

While each of these three types of analysis, oriented at regions, patterns or voxels, uses the same incoming information from activation (BOLD signal modulation), the types of outcome information they provide to the brain researcher are quite different. For this reason, there is no straightforward way of comparing sensitivity of these three approaches. Instead, they can be thought of as encapsulated levels of analysis. This encapsulation can in part be illustrated by the example that Kriegeskorte and Bandettini provide in their Fig. 2. Imagine fMRI data from two experimental conditions. If signal from a region of interest differs between two conditions this could have several reasons. For instance, all voxels could be showing the same degree of difference. Such a difference could be too small to be detected at the single voxel level and it might be grounded in identical patterns expressed with a different gain factor in each of the two conditions. This scenario would justify the use of ROI analyses on sensitivity grounds. However, this difference in ROI activity levels could also arise from qualitatively different activity patterns in its constituent voxels, and such pattern differences might even exist without resulting in net differences averaged across the entire ROI. In this latter case, multi-variate analyses would present a very promising approach to prove that not the entire ROI but elements within it respond differentially to conditions. Again, it might well be that uni-variate analyses provide no statistically significant result in this case.

As a third paradox to be raised in this comment, however, these "pattern analyses" would not go beyond stating that there is a pattern but they would not visualize or define the pattern. In other words, the positive finding of a pattern difference between two conditions that do not yield different average activity levels would still remain blind to the actual pattern underpinning this effect, be that with respect to spatial distribution as well as sign and amplitude of fMRI signal modulations at the voxel level. And the result of a pattern difference could stem from an infinite number of different underlying patterns. Of course, this information is available and could then be extracted, mapped and so on and so forth, but these subsequent steps probably no longer show the same sensitivity benefit as it is naturally inherent to multi-variate analyses.

As we tend to be painfully aware of the limitations in fMRI at the upper resolution limits the previous consideration is maybe more readily illustrated by an example that is already fully within the reach of current fMRI techniques. Just consider the entire brain as a ROI and the two conditions of moving the right and the left index finger. Activity levels across this whole-brain ROI might be indistinguishable between both conditions but pattern analysis would easily discriminate the two. Of course, one would not consider this information satisfactory and proceed to mapping the source of these effects to the left and right motor cortices. At a further level, and this time constrained to the motor cortex, one might find that movements of different fingers can also be distinguished by pattern analyses of activity. Yet, it would again take voxel-based mapping to establish that in primary motor cortex this observation stems from an organizational principle as simple as a continuous gradual somatotopy (Kleinschmidt et al., 1997) instead of for instance putative mosaic patterns or a fractured somatotopy as found in the cerebellum (Nitschke et al., 1996).

So what is the relation between high-resolution fMRI and spatially multi-variate analyses? If a neurophysiological study reports that brain activity differs when looking at a face and a car, that result is trivial from a neurobiological perspective and informative only with respect to the sensitivity of the methods used to assess human brain activity. After all, if a stimulus difference makes a perceptual (and semantic) difference one would expect this to be grounded in different brain activity patterns. If a searchlight approach, as proposed by Kriegeskorte and Bandettini (2007), then narrowed this effect down to cortex in the ventral visual stream this result would be highly compatible with the established insights into functional organisation of the visual processing streams. Yet, it would appear that to know not only *that* a difference in brain activity exists but also *where* (and in which way) it manifests would require a detailed voxel-by-voxel analysis within the searchlight volume. In that sense, one might be predict that a searchlight approach would increase sensitivity but only at the expense of spatial resolution. While this would appear to be in apparent contradiction with the first-glance benefits from high-resolution fMRI, I agree with Kriegeskorte and Bandettini in that this approach might be one of the best reasons for investing into high-resolution fMRI and one of the best ways of successfully exploiting it.

This latter consideration leads to a crucial comment regarding the neuroscientific stake that Kriegeskorte and Bandettini evoke in their contribution. Many aspects of spatially differentiated human brain function will probably forever remain hidden from non-invasive monitoring simply because they occur at the microscopic level. And so far neuroimaging has mostly addressed functional brain organisation at a macroscopic level. Yet, in particular optical imaging for instance in non-human primates has demonstrated an intermediate, mesoscopic, level of functional brain organisation that is often referred to as a 'functional architecture' and that may already be very informative in relation to cognitive processes (see

Tsunoda et al., 2001; Tanaka, 2003). There is glaringly little evidence of such a mesoscopic architecture beyond areas such as early sensory cortices where functional criteria imply a predictable benefit from a structured layout (Chklovskii and Koulakov, 2004) but this lack of knowledge could simply stem from limitations in paradigms studied so far. Indeed, high-resolution fMRI holds promise to successfully address these questions in the future. The aforementioned considerations suggest that in this process pattern analyses would come in as a first-pass exploratory tool that would motivate subsequent mapping procedures. For the latter aspect, voxel-based analyses would inevitably remain an essential component in delineating the mesoscopic structure of functional brain organisation.

Conclusion

In conclusion, this comment revisits the claim that there is something generically special about multi-variate analyses and suggests that they will rather provide a valuable extension to other analytical approaches than entirely replacing them. That magnetic resonance imaging lends itself to a pluralism of methods is one of its major advantages. The variety of signals that can be acquired as well as diverse ways of analyzing these signals can be directly exploited by flexibly adopting on a case-by-case basis the most promising strategy in relation to the individual neurobiological question one seeks to pursue. Success in this pursuit should be the benchmark when assessing the value of methods and it is likely that a diversified repertoire of tools will perform better than even the most powerful of its single elements.

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