**Functional connectivity gradients for accurate and personalized clinical neuroimaging**

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1. **Functional connectivity gradients**
2. **The role of functional connectivity gradients in cognitive dysfunction and lesion-symptom mapping**

*Paragraph showing an extensive number of studies related to clinical cases. Not necessarily with details about each specific finding, but they need to be convincing enough to show that all of them are sort of useless for neurologist or even neurosurgeons.*

So far, mostly descriptive studies. They appear in a wide range of scenarios, from purely structural lesions to highly distributed cognitive and psychiatric disorders. None of them, however, have been able so far to deliver a concise and simple framework promising enough to be moved into the clinics. *Is this true? What are the references that make you think that?*

Therefore, what do we need to move beyond purely phenomenological descriptions and enter the prediction realm? For that, it is crucial to not distinguish, for each clinical scenario, whether the relevant and necessary information should be in terms of diagnosis, prognosis, or treatment monitoring. The former seems a bit redundant, as traditional imaging methods are precise enough for most of the cases. The latter, while interesting, seems to be far-fetched with the current state of the field and functional MRI in general. Instead, focusing our efforts on studying the capabilities of functional connectivity gradients to deliver accurate prognosis should be regarded as the main priority. If they prove reliable, then it naturally follows that they can be used to non-invasively measure several factors related to treatment administration, e.g., progression free survival or the effect of neuro-rehabilitation strategies indicative of health improvements.

1. **Advancing prognostic precision for clinical translation using the robust gradient topology of the human brain**

One of the main advantages of relying on a low dimensional space, is the inherent robustness of the topology of such space. Multiple systems share similar manifolds independently of how noisy the measurements are (REFS). Examples stem from purely theoretical and computational studies to more experimentally based results. Low-dimensional manifolds have been used to predict and understand behavior (REFS), dysfunction (REFS), and even chaos (REFS). Therefore, it comes without much surprise to see that functional connectivity gradients have been shown to be stable across multiple studies since they were introduced almost a decade ago (REFS). Even though studies addressing individual variabilities present within the canonical gradient structures seem to be missing (REFS), it is reasonable to think that the average gradient morphologies derived from large sample sizes (e.g., the human connectome project) represent a fairly accurate description of cortical functional organization revealed by functional MRI (REFS). This, in turn, allows us to rethink this expected and low-variance organization of the cortical profiles of human hemodynamics to provide individualized predictions based on pre-defined markers found by combining patient imaging data and averaged templates derived from high-quality functional MRI data sources (REFS).

Most notoriously, the *disconnectome* in stroke has a long tradition of predicting individual deficits and clinical outcomes by simply overlaying the infarcted regions delineated on the T1-weighted images with a normative tractography map. This normative tractogram can be derived by combining diffusion-weighted data from multiple subjects in the HCP to create an average map of streamlines capturing the most normative white matter pathways of the human brain (REFS). Other recent examples include the definition of normative connectomes to predict deep brain stimulation outcomes (REFS), survival profiles in glioblastomas (REFS), and other psychiatric disorders (REFS). These attempts can create personalized MRI-based markers avoiding the need for expensive acquisitions that compromise clinical translation.

Here, we ask ourselves the question whether a similar concept exists within the functional connectivity gradients research sub-field. Can we draw individual information from the first gradients of human brain function? What biomarkers could be defined based on them and how can they provide robust predictions to clinicians? To this end, we can draw inspiration from structural connectivity and tractography-based efforts to define a normative gradient manifold where individual events may be placed upon to provide personalized predictions.

* 1. **A normative functional connectivity gradient manifold**

The key point that favors the use of functional gradients as opposed to traditional cluster or parcellation-based approaches (e.g., independent component analysis) is that we need not rely on a case-control study to position each patient and the observed clinical variables of interest (REFS). Because the first 3 gradients appear to be sufficiently robust even in the absence of health (REFS), and they can be rigidly aligned to the normative gradient manifold, we can move into a much more direct measurement of brain dysfunctional connectivity than rather plain voxel- or network-based fMRI. Crucially, the variability and intra-class correlation coefficient of which have been thoroughly documented in the literature (REFS).

*We have justified the robustness of the gradients. Now we must define and explain what gradients should be computed (as in how many?), from where (as examples), and how to obtain them.*

* 1. **Markers of brain dysfunction and lesion embedded in normative gradient manifolds**

The Euclidean functional distance marker and its relationship to clinical prognostic factors. It can be localized into a single gradient (e.g., second gradient), this is the marker that is relevant. Because the second gradient is, in general, robust, we can assign any deviation from the norm to a clinical factor.

*Can we speculate about other possible personalized markers that could be defined in this normative gradient manifold? For example, the functional connectivity of the lesion with the rest of the cortical regions. Would this allow us to obtain a personalized pseudo-gradient?*

1. **Immediate challenges for clinical applications**

*A clear definition and study of the minimum prerequisites for trustworthy gradients in health and disease. Is there any study out there that addresses this challenge?*

Furthermore, while nothing prevents the definition of these normative maps from being computed using multiple data sources, the usage of a single healthy template across multiple studies has the potential to reduce data-related biases and artifacts. However, defining multiple normative spaces is advisable to thoroughly assess the exact contribution of the template to the relevant prognostic markers and predictions.

*Individual variability of the gradients and its effect for precision medicine. There are some works with normal fmri, but with gradients? A proper characterization of the inherent variability of the positioning in the manifold would provide a valuable contrast to which to place patient-related data. That is, does the deviation w.r.t. the normative location exceed the expected variations or should instead be assigned to random fluctuations (i.e., unrelated to the pathology at hand).* Alberto: if you create these normative gradients with different number of subjects of the HCP, are they robust?

*Is there a problem with the fact that these sorts of approaches provide personalized information based on indirect measurements?*

*There needs to be a paragraph (at least) dedicated to personal instead of normative approaches. Unclear for now how we could address this.*

**References**

**Author contributions**

**J.F.-R.** Conceptualization, Writing – Original Draft, Writing – Review & Editing, Visualization. **J.K.A.** Conceptualization, Writing – Original Draft, Writing – Review & Editing. **C.K.** Conceptualization, Writing – Original Draft, Writing – Review & Editing.

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