Title: Advancing brain network models to reconcile functional neuroimaging and clinical research

Xenia Kobeleva ^{1,2} , Gaël Varoquaux ³ , Alain Dagher ⁴ , Mohit Adhikari ⁵ , Christian Grefkes ^{6,7} ,
Matthieu Gilson ^{8,9}

Affiliations:

(1) Department of Neurology, University of Bonn, Bonn, Germany

(2) German Center for Neurodegenerative Diseases (DZNE) Bonn, Bonn, Germany

(3) INRIA Saclay, Paris, France

(4) Montreal Neurological Institute, McGill University, Montréal, Canada

(5) Bio-imaging Lab, University of Antwerp, Antwerp, Belgium

(6) Department of Neurology, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

(7) Institute of Neuroscience and Medicine (INM-1, INM-3), Research Centre Juelich, Juelich, Germany

(8) Institute of Neuroscience and Medicine (INM-6) and Institute for Advanced Simulation (IAS-6) and JARA Institute Brain Structure-Function Relationships (INM-10), Jülich Research Centre, Jülich, Germany

(9) Center for Brain and Cognition, Department of Information and Telecommunication technologies, Universitat Pompeu Fabra, Barcelona, Spain

Abstract:

Functional magnetic resonance imaging (fMRI) captures information on brain function beyond anatomical alterations traditionally visible to neuroradiologists. However, the fMRI signal is complex and noisy, and so far fMRI has brought limited value in a clinical research context. We argue that solutions can be found in richer fMRI-based models such as statistical, biophysical and decoding models. These models extract clinically relevant information regarding biological mechanisms and features for classification and prediction (interpretability). Moreover, they are suitable to directly predict clinical variables from their parameters (predictability). We give guidelines for useful applications and pitfalls of such fMRI-based models in a clinical research context, and we look beyond currently used models. In particular, we provide arguments that clinical relevance of fMRI calls for better fMRI activity models incorporating both interpretability and predictability. We illustrate how this synergy of interpretability and predictability can be achieved by combining biophysical models with decoding models. These hybrid models entail reliable and biologically meaningful model parameters. In our view, this synergy is fundamental for the discovery of new pharmacological and interventional targets and the use of models as biomarkers.

1 Neuroimaging in clinical practice and research

1.1 Evolution of neuroimaging diagnostic modalities in neuropsychiatric practice

Medical doctors originally studied and diagnosed diseases based solely on careful observation of symptoms and clinical examination. Several medical technologies, such as laboratory tests and radiographic techniques, had been initially met with skepticism given that they challenged the diagnostic authority of medical practitioners (Berger, 1999) and altered the patient-doctor relationship (Goold and Lipkin, 1999). History tends to repeat itself, and similar discussions are being held nowadays regarding the clinical application of machine learning to neuroimaging signals (Longoni et al., 2019).

Currently, diagnosis using magnetic resonance imaging (MRI) in neurology still mostly relies on qualitative analyses of brain structures and perfusion, which are restricted to anatomical alterations directly visible to the eye. With regard to psychiatry, clinical diagnoses predominantly rely on psychopathological explorations in combination with medical history

and other factors as defined by specific diagnostic manuals such as the Diagnostic and Statistical Manual of Mental Disorders (DSM). Thus far, the clinical utilization of functional MRI (fMRI) does not stretch beyond the identification of localized functional areas for presurgical mapping before epilepsy or tumor surgery (Duffau, 2005; Silva et al., 2018). The broader acceptance of fMRI into clinical diagnostics is partly impeded by a general skepticism regarding the significance of the measured signals (Bennett et al., 2009; Kullmann, 2020), especially when considering the low signal-to-noise-ratio on a single subject level (Gorgolewski et al., 2013). While Blood Oxygen Level-Dependent (BOLD) signals have been clearly shown to indirectly reflect neuronal activity (Shmuel and Leopold, 2008), they have a complex and nonlinear relationship with neuronal information processing and transmission, a relevant measure for mapping neuronal function and dysfunction and understanding neuropsychiatric diseases.

Despite their complex and noisy nature, which further challenges *interpretability*, fMRI data have shown potential for revealing brain dysfunction information not directly visible to the naked eye during an anatomical MRI scan. As increasingly complex signals challenge traditional empirical analyses, various mathematical models have been developed to reproduce the dynamics of fMRI signals and extract information related to cognitive functions or pathological conditions. However, given that these models almost always involve highly multidimensional measures and/or parameterization, their clinical application remains much difficult compared to standard imaging diagnoses (e.g., such identifying lesions in strokes or multiple sclerosis), in which clearly defined normal anatomy is usually established. As such, whether more complex models would be sufficient to make fMRI clinically relevant, especially for neuropsychiatric conditions that still lack robust biological tests, such as psychiatric disorders, still remains unknown.

This opinion article argues that better fMRI activity models are needed to enhance its clinical relevance. We start by providing guidelines on how to ask relevant questions for clinical neurology and psychiatry, applicable to any model in neurology. We then narrow our focus to models and provide an overview of the model types based on or applied to functional brain networks (i.e., considering functional connections of brain regions, such as functional connectivity). Though there are a variety measures derived from BOLD, such as voxel-level activity (mass univariate) or multivariate pattern analysis, we focus our discussion on functional connectivity. Two distinct meanings of *interpretability*—uncovering biological mechanisms versus identifying relevant features in a classifier—are then discussed. In

particular, this paper highlights the need for thorough validation of the relationship between fMRI-based functional connectivity (i.e., pairwise correlations of BOLD signals) and neuronal communication. Moreover, we review the *interpretability* of the models in contrast to *predictability*, herein understood as the ability of a model to predict clinical or cognitive variables from its parameters. We then discuss a promising approach for improving both *predictability* and *interpretability* that combines the strengths of the available models using parameters from biophysical models as features for decoding models (which will be described in more detail later). We finally identify roadblocks and advocate for more careful modeling and robust model validation.

1.2 Asking the right questions using translational research models

The traditional view of translational research mainly encompasses transferring innovative technologies from research into clinical practice (“from bench to bedside”) and vice versa. Newer outlooks on translational research underline the importance of involving the community comprising patients, healthy populations, journalists, and medical practitioners (Cohrs et al., 2014; Forsythe et al., 2016). In the context of using data-driven models in translational research, collaboration between stakeholders can be substantially strengthened by asking precise and clinically relevant research questions. To this end, the “PICO” method (Richardson et al., 1995; Sackett et al., 2000) provides a framework comprising four components: P (population, patient, and/or problem), I (intervention, such as drugs, brain stimulation, diagnostic procedures, exposure, genetic factors), C (intervention for comparison), and O (outcome). A clinical research question is typically presented in the following format:

“In a given patient group, how does the intervention X differ from standard intervention Y in terms of outcome?”

“In a given patient group, how does the diagnostic procedure X differ from standard diagnostic procedure Y in terms of outcome?”

Subsequently, we argue that neuroimaging models could further enhance clinical research, with a collection of examples for each PICO category having been provided below.

1.2.1 Population, patient, and/or problem

One goal of fMRI-based diagnoses is to refine the categories of neuropsychiatric conditions (e.g., identify patient subgroups or individuals at risk) and compare them to standard

categories based on other clinical measures. By doing so, neuroimaging models might help improve patient group selection for the comparison of different disease trajectories (Grefkes and Fink, 2014), namely identifying patients particularly suitable for specific (non-)pharmacological treatments according to treatment response (Dunlop and Mayberg, 2014) or predict different treatment outcomes. Such models might also help identify individuals at risk for certain diseases before the onset of clinical symptoms and thus enable trials on early preventive treatment, which are desperately needed for neurodegenerative diseases, such as Alzheimer's disease.

1.2.2 Intervention/Comparison

fMRI-based measures or models can be tested against standard procedures (e.g., prognosis based on clinical variables) according to whether they improve prognostic or classification accuracy. Some applications of brain activity models have been shown to be clinically useful for assessing cortical functionality after stroke through transcranial magnetic stimulation combined with EEG (Tscherpel et al., 2020), studying regional cerebral diseases to enable targeted treatment in epilepsy surgery (Jirsa et al., 2017), or predicting potential complications of brain tumor resection (Woo et al., 2017). Furthermore, important research on the development of new treatments has aimed to uncover the neuronal mechanisms of neuropathologies, such as quantifying the local and global effects of medications (e.g., on neurotransmitters or neuronal excitability) on brain activity measured using fMRI. To address these concerns, next generation models require a systems medicine approach that possibly also involves animal models (Ren et al., 2014).

1.2.3 Outcome

Models might help create surrogate neuroimaging-based endpoints, such as better regeneration of damaged brain areas determined through MRI, which complement pure clinical endpoints (Prentice, 1989), e.g., long-term functional recovery. By identifying presymptomatic changes, these neuroimaging endpoints could reduce the duration of clinical trials and increase statistical power. To this end, models must capture longitudinal changes in patients' brain activity in order to characterize and determine disease outcomes.

2 Current and emerging models for extracting information from fMRI

Historically, research in modeling fMRI activity has followed two lines: one striving to reproduce and explain the spatiotemporal structure of fMRI signals (e.g., at the whole-brain level) (statistical and biophysical models) and the other focused on extracting relevant information for the classification of patients and controls (decoding models). In the context of functional brain networks, models of fMRI data can be broadly regrouped into three types. Their respective strengths with respect to clinical research objectives (as discussed in Section 1.2) have paved the way for their combination (illustrated on Fig. 1 and discussed in Section 3).

Figure 1: Schematic representation of models applied to functional magnetic resonance imaging data. In a statistical or biophysical model (red box), parameters x are typically tuned to best reproduce the structure of Blood Oxygen Level-Dependent (BOLD) signals y (blue box), maximizing, for example, the likelihood $P(y|x)$ of observing BOLD signals for parameterization x (see the vertical arrow). Predictive models aim to predict clinical labels z (green box; here, two categories are represented by different colored symbols) based on features y derived from BOLD signals (often a function applied to them, such as correlations for functional connectivity, instead of directly using the original signals themselves) or from the estimated model parameters x . Here $P(z|...)$ refers to the

probability that a new sample subject would belong to the category labeled z given the subject's features (y or x). In practice, this probability $P(z|\dots)$ is estimated (and validated) using data with known labels, for example, by training a classifier.

2.1. Statistical generative models: reproducing the BOLD signal and its relevant patterns

Statistical models have long been used to evaluate the neuronal contribution to fMRI signals (Worsley et al., 1996, 1992). More recently, multivariate network models have been used to reproduce the structure of BOLD activity (Baldassarre et al., 2014; Bolton et al., 2018; Varoquaux et al., 2010; Vidaurre et al., 2018). As illustrated in Fig. 1, the model parameters (e.g., network connectivity) are typically optimized to maximize the *goodness of fit* (see the vertical arrow), a measure of the match between empirical signals and their counterpart model signals. The model comes with hypotheses on the spatiotemporal structure of the observed data. Beyond goodness of fit, the model also adds value to clinical applications by determining how its estimated parameters can reliably reflect clinical conditions.

2.2. Biophysical models: uncovering biological mechanisms

Biophysical models, such as dynamic causal modeling (Friston et al., 2003) or dynamic mean field modeling (Deco et al., 2013), have been designed to elucidate the structure of observed BOLD activity, particularly the influence of anatomical (or structural) connectivity (Woolrich and Stephan, 2013). Further details about their structure can be found in infobox 1.

Info box 1: Biophysical models

Biophysical models describe the neuronal dynamics of brain regions and their interactions overlaid onto a model of hemodynamics to generate BOLD signals. The attempt to formalize the link between neuronal activity and fMRI signals is a major point that differentiates biophysical models from statistical functional connectivity models, which directly work at the level of BOLD signals. However, there is no clear boundary between biophysical and statistical models, with several studies falling somewhat in between both models. For instance, studies can use dynamic networks to directly generate the BOLD signals without hemodynamics while constraining their architecture with anatomical data (Gilson et al., 2016). A benefit of hemodynamics-based models, as with dynamic causal modeling, is that they can accommodate deviations from the standard canonical

hemodynamic response function, which is especially useful in neurovascular disorders such as stroke (Grefkes et al., 2008).

With regard to model validation, many whole-brain biophysical models rely on functional connectivity rather than BOLD activation for model fitting (Deco et al., 2013; Ritter et al., 2013). While functional connectivity is typically interpreted as neuronal communication between brain regions, its relationship with neuronal activity has been much less validated than BOLD activation, which has been thoroughly studied, e.g., in animal models (Bartels et al., 2008; David et al., 2008; Ekstrom, 2010). Likewise, relating functional connectivity to biological variables, such as synaptic efficacies, extends well beyond the general concept of communication between brain areas (Buckner, 2010).

Such models have been oriented towards explaining neuropathological BOLD activity by involving specific molecular mechanisms and biological variables, which has been coined as ‘computational psychiatry’ (Stephan and Mathys, 2014; Wang and Krystal, 2014) or ‘computational neurology’ (Maia and Frank, 2011). As an example, recent biophysical models have designed the dynamics of neuronal populations mechanisms in a way that incorporate information from gene expression maps (Murray et al., 2018) or neurotransmitter concentration maps (Demirtaş et al., 2019). Their goal is to mechanistically describe the effect of local variables that can be measured from positron emission tomography or postmortem data on local and global brain activity measured using fMRI. This ability to trace back the effects of biological variables on fMRI measurements is an important part of *interpretability* discussed earlier. A comparison between different types of biophysical models is provided in Fig. 2, where the estimated parameters (in pink boxes) can be seen as a signature of the brain activity state and are chosen to achieve the optimal goodness of fit of the model. Other parameters are derived directly from empirical data (in blue boxes). Note that “complex” models often involve mechanisms with parameters not directly estimated from the analyzed fMRI data but may come from other studies in fundamental science, such as animal models or simply free parameters that are heuristically determined (in green boxes).

Elements of biophysical models

Data-derived and **estimated** parameters (related to fMRI data) and **free** parameters (unrelated to fMRI data, determined using other data)

Figure 2. Elements of biophysical models. The estimated parameters can serve as a representation of BOLD signals, capturing their spatiotemporal structure. They can be used as features in decoding models, thereby searching for biomarkers that characterize brain diseases. Here we consider three types of parameters in the model: local dynamics governed by local parameters (for each ROI), a global parameter, and connectivity between regions of interest. These parameters can be either estimated (in red) or provided by data (in blue). Additionally, free parameters (in green) estimated from other experiments and not directly related to the fMRI data fitted by the model (e.g., firing rates) can be present.

2.3. Decoding models: from fMRI images to clinical phenotypes

A short introduction about decoding models can be found in infobox 2.

Info box 2: Decoding models

Decoding models have been increasingly used in machine learning to predict clinical or cognitive variables from high-dimensional fMRI data (Dadi et al., 2019; Gao et al., 2019; Varoquaux et al., 2017). Practically, such models aim to map input *features*, which may include connectivity measures derived from BOLD signals or estimated parameters in a model as described earlier (see horizontal arrows in Fig. 1), to a *label* (e.g., a phenotype or diagnosis) or a *score* (e.g., cognitive test performance). The corresponding mathematical function from features to labels or scores is initially fit onto a *training set* of data. The generalizability of the prediction is then assessed using its

performance on separate data (*test set*) in a process called *cross-validation* (Varoquaux et al., 2017).

In the same way that biophysical and statistical models are concerned with the goodness of fit of BOLD signals, decoding models are assessed with respect to their prediction performance, which we also refer to as *predictability*. A robust decoding model that predicts a phenotype should ideally provide information regarding which features contribute to the classification, another aspect of *interpretability* mentioned earlier (Pallarés et al., 2018; Yao et al., 2018). For instance, good motor recovery after a stroke can be classified according to primary motor cortex activity within the lesioned hemisphere measured using BOLD-fMRI on the first week after the stroke (Rehme et al., 2015).

Apart from using connectivity measures directly derived from BOLD data, region-wise or seed-based voxel-wise like functional connectivity (Naselaris et al., 2011; Richiardi et al., 2011), more complex metrics (e.g., time-varying functional connectivity) can be used as input for decoding models (Du et al., 2018). Decoding models can be applied to parameters estimated from statistical models, in which the model inversion can be seen as a preprocessing step (see the bottom horizontal arrow in Fig. 1). For instance, the Graphical Lasso can extract pairwise partial correlations among BOLD signals (Varoquaux and Craddock, 2013), resulting in a biomarker formed by a pair of regions with condition-specific changes in functional connectivity. More biologically-driven approaches can be designed by feeding machine learning tools with estimated parameters (e.g., effective connectivity) in a whole-brain dynamic model to predict subject individualities or cognitive states (Brodersen et al., 2011; Gilson et al., 2019; Pallarés et al., 2018). As a representation of BOLD signals, the estimated parameters may not only improve classification, but also yield a distinct interpretation (e.g., restricting the effective connections to anatomically connected regions).

3 Navigating between biophysical and decoding models: potentials and pitfalls

To address relevant questions in clinical research mentioned in Section 1 and establish clinically relevant and efficient biomarkers, we propose to bridge the gap between biophysical network and decoding models in order to combine their respective strengths, good interpretability together with good predictability. We now discuss the potentials and pitfalls of such unified modeling in the clinical environment, focusing on fMRI models.

3.1. Robust decoding needs big data with reliable labels

Decoding models need accurate clinical labels, which can be challenging in itself. In neurology, a combination of medical history, physical examination, and laboratory tests has been used to provide standard classifications of symptoms and diseases that can be utilized as outcome parameters or labels (Bachmann et al., 2005). However, even gold standard clinical evaluations may have limited accuracy, which consequently limits the accuracy attainable by machine learning models. This concern is amplified in rare non-genetic neurological diseases. To start with, diagnosis is often not standardized (Haendel et al., 2020; Klimova et al., 2017), which affects the positive predictive value of a test (i.e., the proportion of true positive results within all positive test results) depending on the prevalence of a disease. Therefore, tests for rare diseases may show a relatively high absolute number of false positives despite excellent test sensitivity (Kohn et al., 2013; Lutgendorf and Stoll, 2016). Consequently, positive predictive values for rare diseases may drop drastically, subsequently compromising the labels for machine learning techniques.

In psychiatry, establishing reliable diagnostic labels is even more challenging considering that laboratory tests are often lacking and patients typically present within a wide range of disease severities. Thus, labeling is subject to the interpretation of clinicians who rely mostly on symptom-based diagnostic criteria (as proposed in disease classification manuals provided by different organizations, such as the Diagnostic and Statistical Manual of Mental Disorders, DSM).

However, the imperfection of clinical labels is not, by itself, an obstacle in developing useful neuroimaging biomarkers. Measures, such as repeated testing, can certainly improve the reliability of a training set given a sufficient sample size. Provided that such repeated tests do not have considerable variability, a classifier can learn to do better than the original clinical labels and thus enhance diagnostic accuracy (Wickenberg-Bolin et al., 2006).

Small sample sizes have been a well-known problem for machine learning techniques (Chu et al., 2012; Varoquaux, 2018). For complex data, machine learning techniques can only achieve good accuracy by using very large datasets to train the corresponding decoding model (Huf et al., 2014; Varoquaux, 2018), similar to automated image recognition approaches using deep learning (Nguyen et al., 2020). Big data for neuropsychiatric diseases thus requires the alignment of diverse datasets in terms of neuroimaging (acquired

using different scanners or protocols), as well as diagnostic criteria and clinical measures (Abraham et al., 2017; Karrer et al., 2019; Pomponio et al., 2020; Tax et al., 2019; Westeneng et al., 2018; Yamashita et al., 2019). Big-data approaches may not be easily applicable to rare or severe diseases, for which a sufficient number of cases is difficult to obtain. As such, a potential solution might be to group patients according to symptoms across different diagnostic categories or increase the number of measurements per subject to compensate for the small sample sizes (Krischer et al., 2014).

3.2. Personalized medicine requires tackling heterogeneity

A one-size-fits-all model of a disease might be helpful for understanding general disease pathophysiology and developing novel therapeutic targets at a group level. However, establishing a prognosis that can be useful across various patients requires a given model to integrate the evolution of different disease phenotypes and relevant patient characteristics. This means that the identifiability of the model parameters should be accessible in practice from data obtained from a single patient over, at most, a few fMRI recording sessions considering the well-known issues of signal-to-noise in fMRI data (Gorgolewski et al., 2013).

fMRI studies easily suffer from selection bias. Most clinical trials have strict inclusion and exclusion criteria, resulting in patient groups that are not representative of the general patient population. In the field of stroke research, for instance, fMRI studies typically lack patients with very severe neurological deficits, given their inability to provide informed consent for a scientific study or lay still for a certain amount of time inside the scanner (Dani et al., 2008; Hotter et al., 2017). Therefore, most conclusions obtained from stroke fMRI studies only apply to conscious, cooperative, mildly-to-moderately affected patients. Studies of neurodegenerative diseases face similar external-validity challenges: movement disorders some patients (e.g. tremors) interfere with MRI acquisition. Hence findings from fMRI clinical trials might be less applicable to patients with very severe neurological symptoms or atypical disease phenotypes (Mariani et al., 2019). Developing models on less severe symptoms that extrapolate to severe cases could be used to infer clinical outcomes for these (Salvalaggio et al., 2020).

Beyond the selection bias of fMRI studies, a given study cohort often displays a large heterogeneity. Numerous patients suffer from multiple diseases (e.g., a patient with dementia having recurrent strokes, a pacemaker, and lung cancer or a patient with depression, as well as personality and addiction disorders). The problem with non-homogeneous samples is

further complicated by interindividual differences in drug treatment, with some drugs interfering with BOLD signals such as certain neuroleptics (Röder et al., 2010), as well as the complex interactions resulting from taking multiple drugs. Such multimorbidity and polypharmacy has remained a considerable problem in clinical studies, that can only be addressed through very large samples, which make studies exceedingly expensive, long-lasting, and complicated to organize. One important step to address such concerns has been population-based approaches like the UK Biobank study (Elliott et al., 2018; Ward et al., 2019) and the use of normative models (Marquand et al., 2016). However, remains the problem of the considerably large fraction of patients that cannot be included into an MRI study due to contraindications, such as non-MRI-compatible pacemakers, metal splints, or implanted electrodes for deep brain stimulations. For such patients, other techniques for obtaining brain activity should be explored, such as near infrared spectroscopy or EEG-based techniques. Different neuroimaging signals must then be aligned, for instance using functional connectivity from fMRI and EEG in the same analysis.

Lastly, fMRI is fragile in conditions with altered BOLD signals or altered neurovascular coupling as encountered in the case of altered vessel status, such as atherosclerosis, leading to narrowing or occlusion of vessels. These conditions can be frequently encountered in older populations and may be clinically silent and cannot be inferred from BOLD-sensitive images (e.g., gradient-echo T2*) post-hoc.

Therefore, fMRI studies with patients or older individuals should ideally always include diagnostic scans to ensure the validity of BOLD signals computed from fMRI volumes. Currently, using anatomical information (e.g., atrophy) plotted onto a normative connectome to predict functional connectivity patterns can be used as a workaround (Corp et al., 2019; Horn et al., 2017). Ideally, future models should incorporate corrected function of the hemodynamic response in the case of lesions or atrophy.

3.3. Bridging interpretability and predictability to uncover pathomechanisms as a basis for therapy

Figure 3. Focussing on good prediction alone may not provide information on mechanisms and vice versa, but both need to be combined. Using a biophysical model that involves mechanisms that can also be informed by other neuroimaging modalities (e.g., neurotransmitters) or data from animal studies may be useful to extract relevant information from fMRI data, for instance, by estimating parameters that characterize the brain state. This signature (or representation of BOLD signals) can then be used as features for decoding models with the aim of achieving a sweet spot between interpretability and predictability.

Beyond leading to accurate prediction, models for clinical research should also be interpretable (see Figure 3). We discuss two distinct meanings of interpretability: understanding the important features and unraveling biological mechanisms. The first meaning of interpretability can be achieved by understanding the informative features of decoding models and leads to the identification of relevant brain regions for disease understanding (Hoyos-Ildrobo et al., 2018). For instance, interpretable architectures can reconstruct inverse images of interesting labels from deep neural networks into brain anatomical regions (Böhle et al., 2019). This type of interpretability has several benefits in the context of translational research. It can be used to detect hidden biases through careful model validation by applying the model to new data. Furthermore, the evaluation and

correction of potential prediction errors allows clinicians to consider disease severity and adverse effects when choosing the appropriate treatment (e.g., delaying treatment due to the risk of developing a brain tumor vs. undergoing a risky treatment for migraine headache).

The second meaning of interpretability, in the sense of mechanistic interpretation, can be achieved by integrating biologically meaningful parameters estimated from other imaging modalities (e.g. neurotransmitter concentration) into the modelled brain dynamics. This is key to developing pharmaceuticals based on the manipulation of physiological mechanisms that lead to the altered brain dynamics. However, to be used in clinical research, models including different data sources for parameter estimation should be aligned. As an example, effective connectivity may quantitatively and qualitatively differ according to whether or not the model includes neurotransmitter concentrations. In biophysical whole-brain models, the structure of empirical BOLD signals (e.g., functional connectivity) can be determined via the estimated parameters whose numbers may vary dramatically across different models. For instance, effective connectivity in a whole-brain model can provide a rich representation of BOLD dynamics involving thousands of estimated weights (Frässle et al., 2018; Gilson et al., 2019), similar to the statistical models mentioned previously. In contrast, model fitting may involve only a few parameters, such as a single global coupling parameter in the original mean field model (Deco et al., 2013), or several parameters that determine highly nonlinear nodal dynamics (Proix et al., 2017).

In any case, such biophysical models have to be *identifiable* with respect to their fitting procedure (Wilson and Collins, 2019). This should be checked using parameter recovery (e.g., creating simulated data with known parameters and fitting a model to estimate these parameters), to ensure that the estimated parameters in the model unambiguously represent the reproduced BOLD structure. These estimated parameters can be used as features in decoding models, which establishes solid interpretations on brain activity. *Identifiability* is all the more crucial when parameters are estimated in increasingly complex models, such as those that aim to comprehensively describe pathological alterations of neuronal activity involving neurotransmitters (see Fig. 2). Free parameters with no relationship to the data are often present when linking diverse data types in a model, which may affect the estimation of other parameters and necessitates control using robustness checks. These checks ensure similar results across different variations of biophysical models and generalizability of estimated parameters using out-of-sample data.

Given robust parameters across different data types, biophysical models could be synergistically combined with decoding models. In that way their respective strengths can be combined in a next generation of biophysical models that inform on the biological mechanisms which are relevant for prediction, as illustrated in Fig. 3. This will allow for a translation from pure machine-learning diagnosis to a further level of model-based prediction. In our view this new generation of models will be able to achieve a balance between interpretability (both in terms of identification of relevant features and mechanistic interpretation) and predictability of clinical outcome. The key is to identify biologically meaningful data-based and estimated parameters that represent the brain activity state. Using these estimated parameters as features for decoding models can build dynamical signatures. A step in that direction has been made in the field by designing models of effective connectivity that give good prediction accuracy (Brodersen et al., 2011; Frässle et al., 2018; Gilson et al., 2019). Using these new types of models will allow exploring meaningful therapeutic pharmacological or interventional targets beyond the localization of brain regions with strongest changes in BOLD activity or functional connectivity interactions.

4 Perspective: bringing models into clinical practice

Looking to the future, large neuroimaging datasets covering many diseases will bring better models of fMRI activity, that contribute to improving diagnosis and treatment in neurology and psychiatry. Models suited to clinical applications must not only capture better BOLD activity, for instance via functional connectivity, but also the influence of other biological factors, such as neurotransmitters, proteins, and genes. A critical limitation for clinical applicability lies in the noisy and heterogeneous nature of patients' data. As models improve to capture this heterogeneity, they will gradually become useful tools for clinicians, supporting decision making, although they should not replace clinical reasoning. They could constitute an additional element within a set of established diagnostic procedures and might increase the certainty of a diagnostic classification or risk assessment through the use of multimodal decision support systems. To improve functionality, these models should be connected with more complete electronic health records to extract additional patient data and visually present the results of the analysis, for example, through secure and flexible web services (Khalilia et al., 2015). Broader involvement would require additional training for dedicated medical personnel in model-based data analyses, in the same manner as MRI physicists.

Using increasingly sensitive models of brain activity for clinical practice has opportunities for early treatment but also ethical consequences. Similar to the situation of presymptomatic

genetic testing, doctors and patients might face the challenge of discussing a diagnosis of a presymptomatic neuropsychiatric disease based solely on a possibly complex model without any visible brain pathology. What's more, there are direct consequences on the daily life of patients affecting career choice, family planning, and health insurance policies, as well as have psychological consequences (Godino et al., 2016; Tibben et al., 1997). Therefore, ethical guidelines must be developed alongside the models to assess the potential benefit and risks of communicating the model results to the patients.

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References

- Abraham, A., Milham, M.P., Di Martino, A., Craddock, R.C., Samaras, D., Thirion, B., Varoquaux, G., 2017. Deriving reproducible biomarkers from multi-site resting-state data: An Autism-based example. *NeuroImage* 147, 736–745. <https://doi.org/10.1016/j.neuroimage.2016.10.045>
- Bachmann, L.M., Jüni, P., Reichenbach, S., Ziswiler, H.-R., Kessels, A.G., Vögelin, E., 2005. Consequences of different diagnostic 'gold standards' in test accuracy research: Carpal Tunnel Syndrome as an example. *Int. J. Epidemiol.* 34, 953–955. <https://doi.org/10.1093/ije/dyi105>
- Baldassarre, A., Ramsey, L., Hacker, C.L., Callejas, A., Astafiev, S.V., Metcalf, N.V., Zinn, K., Rengachary, J., Snyder, A.Z., Carter, A.R., Shulman, G.L., Corbetta, M., 2014. Large-scale changes in network interactions as a physiological signature of spatial neglect. *Brain* 137, 3267–3283. <https://doi.org/10.1093/brain/awu297>
- Bartels, A., Logothetis, N.K., Moutoussis, K., 2008. fMRI and its interpretations: an illustration on directional selectivity in area V5/MT. *Trends Neurosci.* 31, 444–453. <https://doi.org/10.1016/j.tins.2008.06.004>
- Bennett, C.M., Wolford, G.L., Miller, M.B., 2009. The principled control of false positives in neuroimaging. *Soc. Cogn. Affect. Neurosci.* 4, 417–422. <https://doi.org/10.1093/scan/nsp053>
- Berger, D., 1999. A brief history of medical diagnosis and the birth of the clinical laboratory. Part 1--Ancient times through the 19th century. *MLO. Med. Lab. Obs.* 31, 28–30, 32, 34–40.
- Böhle, M., Eitel, F., Weygandt, M., Ritter, K., 2019. Layer-Wise Relevance Propagation for Explaining Deep Neural Network Decisions in MRI-Based Alzheimer's Disease Classification. *Front. Aging Neurosci.* 11, 194. <https://doi.org/10.3389/fnagi.2019.00194>
- Bolton, T.A.W., Tarun, A., Sterpenich, V., Schwartz, S., Van De Ville, D., 2018. Interactions Between Large-Scale Functional Brain Networks are Captured by Sparse Coupled HMMs. *IEEE Trans. Med. Imaging* 37, 230–240. <https://doi.org/10.1109/TMI.2017.2755369>
- Brodersen, K.H., Schofield, T.M., Leff, A.P., Ong, C.S., Lomakina, E.I., Buhmann, J.M.,

- Stephan, K.E., 2011. Generative Embedding for Model-Based Classification of fMRI Data. *PLoS Comput. Biol.* 7, e1002079. <https://doi.org/10.1371/journal.pcbi.1002079>
- Buckner, R.L., 2010. Human functional connectivity: New tools, unresolved questions. *Proc. Natl. Acad. Sci.* 107, 10769. <https://doi.org/10.1073/pnas.1005987107>
- Chu, C., Hsu, A.-L., Chou, K.-H., Bandettini, P., Lin, C., 2012. Does feature selection improve classification accuracy? Impact of sample size and feature selection on classification using anatomical magnetic resonance images. *NeuroImage* 60, 59–70. <https://doi.org/10.1016/j.neuroimage.2011.11.066>
- Cohrs, R.J., Martin, T., Ghahramani, P., Bidaut, L., Higgins, P.J., Shahzad, A., 2014. Translational Medicine definition by the European Society for Translational Medicine. *Eur. J. Mol. Clin. Med.* 2, 86. <https://doi.org/10.1016/j.nhtm.2014.12.002>
- Corp, D.T., Joutsa, J., Darby, R.R., Delnooz, C.C.S., van de Warrenburg, B.P.C., Cooke, D., Prudente, C.N., Ren, J., Reich, M.M., Batla, A., Bhatia, K.P., Jinnah, H.A., Liu, H., Fox, M.D., 2019. Network localization of cervical dystonia based on causal brain lesions. *Brain J. Neurol.* 142, 1660–1674. <https://doi.org/10.1093/brain/awz112>
- Dadi, K., Rahim, M., Abraham, A., Chyzhyk, D., Milham, M., Thirion, B., Varoquaux, G., Alzheimer's Disease Neuroimaging Initiative, 2019. Benchmarking functional connectome-based predictive models for resting-state fMRI. *NeuroImage* 192, 115–134. <https://doi.org/10.1016/j.neuroimage.2019.02.062>
- Dani, K.A., McCormick, M.T., Muir, K.W., 2008. Brain lesion volume and capacity for consent in stroke trials: potential regulatory barriers to the use of surrogate markers. *Stroke* 39, 2336–2340. <https://doi.org/10.1161/STROKEAHA.107.507111>
- David, O., Guillemain, I., Sallet, S., Reyt, S., Deransart, C., Segebarth, C., Depaulis, A., 2008. Identifying Neural Drivers with Functional MRI: An Electrophysiological Validation. *PLoS Biol.* 6. <https://doi.org/10.1371/journal.pbio.0060315>
- Deco, G., Ponce-Alvarez, A., Mantini, D., Romani, G.L., Hagmann, P., Corbetta, M., 2013. Resting-state functional connectivity emerges from structurally and dynamically shaped slow linear fluctuations. *J. Neurosci. Off. J. Soc. Neurosci.* 33, 11239–52. <https://doi.org/10.1523/JNEUROSCI.1091-13.2013>
- Demirtaş, M., Burt, J.B., Helmer, M., Ji, J.L., Adkinson, B.D., Glasser, M.F., Van Essen, D.C., Sotiropoulos, S.N., Anticevic, A., Murray, J.D., 2019. Hierarchical Heterogeneity across Human Cortex Shapes Large-Scale Neural Dynamics. *Neuron* 101, 1181–1194.e13. <https://doi.org/10.1016/j.neuron.2019.01.017>
- Du, Y., Fu, Z., Calhoun, V.D., 2018. Classification and Prediction of Brain Disorders Using Functional Connectivity: Promising but Challenging. *Front. Neurosci.* 12. <https://doi.org/10.3389/fnins.2018.00525>
- Duffau, H., 2005. Lessons from brain mapping in surgery for low-grade glioma: insights into associations between tumour and brain plasticity. *Lancet Neurol.* 4, 476–486. [https://doi.org/10.1016/S1474-4422\(05\)70140-X](https://doi.org/10.1016/S1474-4422(05)70140-X)
- Dunlop, B.W., Mayberg, H.S., 2014. Neuroimaging-based biomarkers for treatment selection in major depressive disorder. *Dialogues Clin. Neurosci.* 16, 479–490.
- Ekstrom, A., 2010. How and when the fMRI BOLD signal relates to underlying neural activity: the danger in dissociation. *Brain Res. Rev.* 62, 233–244. <https://doi.org/10.1016/j.brainresrev.2009.12.004>
- Elliott, L.T., Sharp, K., Alfaro-Almagro, F., Shi, S., Miller, K.L., Douaud, G., Marchini, J., Smith, S.M., 2018. Genome-wide association studies of brain imaging phenotypes in UK Biobank. *Nature* 562, 210. <https://doi.org/10.1038/s41586-018-0571-7>
- Forsythe, L.P., Ellis, L.E., Edmundson, L., Sabharwal, R., Rein, A., Konopka, K., Frank, L., 2016. Patient and Stakeholder Engagement in the PCORI Pilot Projects: Description and Lessons Learned. *J. Gen. Intern. Med.* 31, 13–21. <https://doi.org/10.1007/s11606-015-3450-z>

- Frässle, S., Lomakina, E.I., Kasper, L., Manjaly, Z.M., Leff, A., Pruessmann, K.P., Buhmann, J.M., Stephan, K.E., 2018. A generative model of whole-brain effective connectivity. *NeuroImage* 179, 505–529. <https://doi.org/10.1016/j.neuroimage.2018.05.058>
- Friston, K.J., Harrison, L., Penny, W., 2003. Dynamic causal modelling. *NeuroImage* 19, 1273–1302.
- Gao, S., Greene, A.S., Constable, R.T., Scheinost, D., 2019. Combining multiple connectomes improves predictive modeling of phenotypic measures. *NeuroImage* 201, 116038. <https://doi.org/10.1016/j.neuroimage.2019.116038>
- Gilson, M., Moreno-Bote, R., Ponce-Alvarez, A., Ritter, P., Deco, G., 2016. Estimation of Directed Effective Connectivity from fMRI Functional Connectivity Hints at Asymmetries of Cortical Connectome. *PLOS Comput. Biol.* 12, e1004762. <https://doi.org/10.1371/journal.pcbi.1004762>
- Gilson, M., Zamora-López, G., Pallarés, V., Adhikari, M.H., Senden, M., Campo, A.T., Mantini, D., Corbetta, M., Deco, G., Insabato, A., 2019. Model-based whole-brain effective connectivity to study distributed cognition in health and disease. *Netw. Neurosci.* 4, 338–373. https://doi.org/10.1162/netn_a_00117
- Godino, L., Turchetti, D., Jackson, L., Hennessy, C., Skirton, H., 2016. Impact of presymptomatic genetic testing on young adults: a systematic review. *Eur. J. Hum. Genet.* 24, 496–503. <https://doi.org/10.1038/ejhg.2015.153>
- Goold, S.D., Lipkin, M., 1999. The Doctor–Patient Relationship. *J. Gen. Intern. Med.* 14, S26–S33. <https://doi.org/10.1046/j.1525-1497.1999.00267.x>
- Gorgolewski, K.J., Storkey, A.J., Bastin, M.E., Whittle, I., Pernet, C., 2013. Single subject fMRI test–retest reliability metrics and confounding factors. *NeuroImage* 69, 231–243. <https://doi.org/10.1016/j.neuroimage.2012.10.085>
- Grefkes, C., Fink, G.R., 2014. Connectivity-based approaches in stroke and recovery of function. *Lancet Neurol.* 13, 206–216. [https://doi.org/10.1016/S1474-4422\(13\)70264-3](https://doi.org/10.1016/S1474-4422(13)70264-3)
- Grefkes, C., Nowak, D.A., Eickhoff, S.B., Dafotakis, M., Küst, J., Karbe, H., Fink, G.R., 2008. Cortical connectivity after subcortical stroke assessed with functional magnetic resonance imaging. *Ann. Neurol.* 63, 236–246. <https://doi.org/10.1002/ana.21228>
- Haendel, M., Vasilevsky, N., Unni, D., Bologa, C., Harris, N., Rehm, H., Hamosh, A., Baynam, G., Groza, T., McMurry, J., Dawkins, H., Rath, A., Thaxon, C., Bocci, G., Joachimiak, M.P., Köhler, S., Robinson, P.N., Mungall, C., Oprea, T.I., 2020. How many rare diseases are there? *Nat. Rev. Drug Discov.* 19, 77–78. <https://doi.org/10.1038/d41573-019-00180-y>
- Horn, A., Reich, M., Vorwerk, J., Li, N., Wenzel, G., Fang, Q., Schmitz-Hübsch, T., Nickl, R., Kupsch, A., Volkmann, J., Kühn, A.A., Fox, M.D., 2017. Connectivity Predicts Deep Brain Stimulation Outcome in Parkinson Disease. *Ann. Neurol.* 82, 67–78. <https://doi.org/10.1002/ana.24974>
- Hotter, B., Ulm, L., Hoffmann, S., Katan, M., Montaner, J., Bustamante, A., Meisel, A., 2017. Selection bias in clinical stroke trials depending on ability to consent. *BMC Neurol.* 17. <https://doi.org/10.1186/s12883-017-0989-9>
- Hoyos-Idrobo, A., Varoquaux, G., Schwartz, Y., Thirion, B., 2018. FReM – Scalable and stable decoding with fast regularized ensemble of models. *NeuroImage, New advances in encoding and decoding of brain signals* 180, 160–172. <https://doi.org/10.1016/j.neuroimage.2017.10.005>
- Huf, W., Kalcher, K., Boubela, R.N., Rath, G., Vecsei, A., Filzmoser, P., Moser, E., 2014. On the generalizability of resting-state fMRI machine learning classifiers. *Front. Hum. Neurosci.* 8. <https://doi.org/10.3389/fnhum.2014.00502>
- Jirsa, V.K., Proix, T., Perdikis, D., Woodman, M.M., Wang, H., Gonzalez-Martinez, J., Bernard, C., Bénar, C., Guye, M., Chauvel, P., Bartolomei, F., 2017. The Virtual

- Epileptic Patient: Individualized whole-brain models of epilepsy spread. *NeuroImage* 145, 377–388. <https://doi.org/10.1016/j.neuroimage.2016.04.049>
- Karrer, T.M., Bassett, D.S., Derntl, B., Gruber, O., Aleman, A., Jardri, R., Laird, A.R., Fox, P.T., Eickhoff, S.B., Grisel, O., Varoquaux, G., Thirion, B., Bzdok, D., 2019. Brain-based ranking of cognitive domains to predict schizophrenia. *Hum. Brain Mapp.* 40, 4487–4507. <https://doi.org/10.1002/hbm.24716>
- Khalilia, M., Choi, M., Henderson, A., Iyengar, S., Braunstein, M., Sun, J., 2015. Clinical Predictive Modeling Development and Deployment through FHIR Web Services. *AMIA. Annu. Symp. Proc.* 2015, 717–726.
- Klimova, B., Storek, M., Kuca *, M.V. and K., 2017. Global View on Rare Diseases: A Mini Review [WWW Document]. *Curr. Med. Chem.* URL <https://www.eurekaselect.com/152362/article> (accessed 2.3.21).
- Kohn, M.A., Carpenter, C.R., Newman, T.B., 2013. Understanding the Direction of Bias in Studies of Diagnostic Test Accuracy. *Acad. Emerg. Med.* 20, 1194–1206. <https://doi.org/10.1111/acem.12255>
- Krischer, J.P., Gopal-Srivastava, R., Graft, S.C., Eckstein, D.J., Rare Diseases Clinical Research Network, 2014. The Rare Diseases Clinical Research Network's organization and approach to observational research and health outcomes research. *J. Gen. Intern. Med.* 29 Suppl 3, S739-744. <https://doi.org/10.1007/s11606-014-2894-x>
- Kullmann, D.M., 2020. Editorial. *Brain* 143, 1045–1045. <https://doi.org/10.1093/brain/awaa082>
- Longoni, C., Bonezzi, A., Morewedge, C.K., 2019. Resistance to Medical Artificial Intelligence. *J. Consum. Res.* 46, 629–650. <https://doi.org/10.1093/jcr/ucz013>
- Lutgendorf, M.A., Stoll, K.A., 2016. Why 99% may not be as good as you think it is: limitations of screening for rare diseases. *J. Matern.-Fetal Neonatal Med. Off. J. Eur. Assoc. Perinat. Med. Fed. Asia Ocean. Perinat. Soc. Int. Soc. Perinat. Obstet.* 29, 1187–1189. <https://doi.org/10.3109/14767058.2015.1039977>
- Maia, T.V., Frank, M.J., 2011. From reinforcement learning models to psychiatric and neurological disorders. *Nat. Neurosci.* 14, 154–162. <https://doi.org/10.1038/nn.2723>
- Mariani, L.-L., Guimarães-Costa, R., Grabli, D., Le Toullec, B., Cormier-Dequaire, F., Degos, B., Dubois, B., Vidailhet, M., Lacomblez, L., Corvol, J.-C., 2019. Are PSP patients included in clinical trials representative of the general PSP population? *Parkinsonism Relat. Disord.* 66, 202–206. <https://doi.org/10.1016/j.parkreldis.2019.07.012>
- Marquand, A.F., Rezek, I., Buitelaar, J., Beckmann, C.F., 2016. Understanding Heterogeneity in Clinical Cohorts Using Normative Models: Beyond Case-Control Studies. *Biol. Psychiatry* 80, 552–561. <https://doi.org/10.1016/j.biopsych.2015.12.023>
- Murray, J.D., Demirtaş, M., Anticevic, A., 2018. Biophysical Modeling of Large-Scale Brain Dynamics and Applications for Computational Psychiatry. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* 3, 777–787. <https://doi.org/10.1016/j.bpsc.2018.07.004>
- Naselaris, T., Kay, K.N., Nishimoto, S., Gallant, J.L., 2011. Encoding and decoding in fMRI. *NeuroImage* 56, 400–410. <https://doi.org/10.1016/j.neuroimage.2010.07.073>
- Nguyen, M., He, T., An, L., Alexander, D.C., Feng, J., Yeo, B.T.T., 2020. Predicting Alzheimer's disease progression using deep recurrent neural networks. *NeuroImage* 222, 117203. <https://doi.org/10.1016/j.neuroimage.2020.117203>
- Pallarés, V., Insabato, A., Sanjuán, A., Kühn, S., Mantini, D., Deco, G., Gilson, M., 2018. Extracting orthogonal subject- and condition-specific signatures from fMRI data using whole-brain effective connectivity. *NeuroImage* 178, 238–254. <https://doi.org/10.1016/j.neuroimage.2018.04.070>
- Pomponio, R., Erus, G., Habes, M., Doshi, J., Srinivasan, D., Mamourian, E., Bashyam, V., Nasrallah, I.M., Satterthwaite, T.D., Fan, Y., Launer, L.J., Masters, C.L., Maruff, P.,

- Zhuo, C., Völzke, H., Johnson, S.C., Fripp, J., Koutsouleris, N., Wolf, D.H., Gur, Raquel, Gur, Ruben, Morris, J., Albert, M.S., Grabe, H.J., Resnick, S.M., Bryan, R.N., Wolk, D.A., Shinohara, R.T., Shou, H., Davatzikos, C., 2020. Harmonization of large MRI datasets for the analysis of brain imaging patterns throughout the lifespan. *NeuroImage* 208, 116450. <https://doi.org/10.1016/j.neuroimage.2019.116450>
- Prentice, R.L., 1989. Surrogate endpoints in clinical trials: Definition and operational criteria. *Stat. Med.* 8, 431–440. <https://doi.org/10.1002/sim.4780080407>
- Proix, T., Bartolomei, F., Guye, M., Jirsa, V.K., 2017. Individual brain structure and modelling predict seizure propagation. *Brain* 140, 641–654. <https://doi.org/10.1093/brain/awx004>
- Rehme, A.K., Volz, L.J., Feis, D.-L., Bomilcar-Focke, I., Liebig, T., Eickhoff, S.B., Fink, G.R., Grefkes, C., 2015. Identifying Neuroimaging Markers of Motor Disability in Acute Stroke by Machine Learning Techniques. *Cereb. Cortex N. Y. N 1991* 25, 3046–3056. <https://doi.org/10.1093/cercor/bhu100>
- Ren, C., Guingab-Cagmat, J., Kobeissy, F., Zoltewicz, S., Mondello, S., Gao, M., Hafeez, A., Li, N., Geng, X., Larner, S.F., Anagli, J., Hayes, R.L., Ji, X., Ding, Y., 2014. A neuroproteomic and systems biology analysis of rat brain post intracerebral hemorrhagic stroke. *Brain Res. Bull.* 102, 46–56. <https://doi.org/10.1016/j.brainresbull.2014.02.005>
- Richardson, W.S., Wilson, M.C., Nishikawa, J., Hayward, R.S., 1995. The well-built clinical question: a key to evidence-based decisions. *ACP J. Club* 123, A12-13.
- Richiardi, J., Eryilmaz, H., Schwartz, S., Vuilleumier, P., Van De Ville, D., 2011. Decoding brain states from fMRI connectivity graphs. *NeuroImage, Multivariate Decoding and Brain Reading* 56, 616–626. <https://doi.org/10.1016/j.neuroimage.2010.05.081>
- Ritter, P., Schirner, M., McIntosh, A.R., Jirsa, V.K., 2013. The Virtual Brain Integrates Computational Modeling and Multimodal Neuroimaging. *Brain Connect.* 3, 121–145. <https://doi.org/10.1089/brain.2012.0120>
- Röder, C.H., Hoogendam, J.M., van der Veen, F.M., 2010. FMRI, antipsychotics and schizophrenia. Influence of different antipsychotics on BOLD-signal. *Curr. Pharm. Des.* 16, 2012–2025. <https://doi.org/10.2174/138161210791293088>
- Sackett, D.L., Straus, S.E., Haynes, B.R., Rosenberg, W., Richardson, W.S., 2000. Evidence-Based Medicine: How to Practice and Teach EBM (Book with CD-ROM): Amazon.co.uk: David L. Sackett, Sharon E. Straus MD Dr., W. Scott Richardson MD Dr., William Rosenberg, R. Brian Haynes MD Dr.: 9780443062407: Books, 2. ed. Churchill Livingstone.
- Salvalaggio, A., De Filippo De Grazia, M., Zorzi, M., Thiebaut de Schotten, M., Corbetta, M., 2020. Post-stroke deficit prediction from lesion and indirect structural and functional disconnection. *Brain* 143, 2173–2188. <https://doi.org/10.1093/brain/awaa156>
- Shmuel, A., Leopold, D.A., 2008. Neuronal correlates of spontaneous fluctuations in fMRI signals in monkey visual cortex: Implications for functional connectivity at rest. *Hum. Brain Mapp.* 29, 751–761. <https://doi.org/10.1002/hbm.20580>
- Silva, M.A., See, A.P., Essayed, W.I., Golby, A.J., Tie, Y., 2018. Challenges and techniques for presurgical brain mapping with functional MRI. *NeuroImage Clin.* 17, 794–803. <https://doi.org/10.1016/j.nicl.2017.12.008>
- Stephan, K.E., Mathys, C., 2014. Computational approaches to psychiatry. *Curr. Opin. Neurobiol.* 25, 85–92. <https://doi.org/10.1016/j.conb.2013.12.007>
- Tax, C.M., Grussu, F., Kaden, E., Ning, L., Rudrapatna, U., John Evans, C., St-Jean, S., Leemans, A., Koppers, S., Merhof, D., Ghosh, A., Tanno, R., Alexander, D.C., Zappalà, S., Charron, C., Kusmia, S., Linden, D.E., Jones, D.K., Veraart, J., 2019. Cross-scanner and cross-protocol diffusion MRI data harmonisation: A benchmark database and evaluation of algorithms. *NeuroImage* 195, 285–299.

- <https://doi.org/10.1016/j.neuroimage.2019.01.077>
- Tibben, A., Roos, R. a. C., Niermeijer, M.F., 1997. Psychological consequences of presymptomatic testing for Huntington's disease. *The Lancet* 349, 809. [https://doi.org/10.1016/S0140-6736\(05\)60242-5](https://doi.org/10.1016/S0140-6736(05)60242-5)
- Tscherpel, C., Dern, S., Hensel, L., Ziemann, U., Fink, G.R., Grefkes, C., 2020. Brain responsivity provides an individual readout for motor recovery after stroke. *Brain* 143, 1873–1888. <https://doi.org/10.1093/brain/awaa127>
- Varoquaux, G., 2018. Cross-validation failure: Small sample sizes lead to large error bars. *NeuroImage* 180, 68–77. <https://doi.org/10.1016/j.neuroimage.2017.06.061>
- Varoquaux, G., Baronnet, F., Kleinschmidt, A., Fillard, P., Thirion, B., 2010. Detection of brain functional-connectivity difference in post-stroke patients using group-level covariance modeling. *Med. Image Comput. Comput.-Assist. Interv. MICCAI Int. Conf. Med. Image Comput. Comput.-Assist. Interv.* 13, 200–208. https://doi.org/10.1007/978-3-642-15705-9_25
- Varoquaux, G., Craddock, R.C., 2013. Learning and comparing functional connectomes across subjects. *NeuroImage, Mapping the Connectome* 80, 405–415. <https://doi.org/10.1016/j.neuroimage.2013.04.007>
- Varoquaux, G., Raamana, P.R., Engemann, D.A., Hoyos-Idrobo, A., Schwartz, Y., Thirion, B., 2017. Assessing and tuning brain decoders: Cross-validation, caveats, and guidelines. *NeuroImage, Individual Subject Prediction* 145, 166–179. <https://doi.org/10.1016/j.neuroimage.2016.10.038>
- Vidaurre, D., Abeysuriya, R., Becker, R., Quinn, A.J., Alfaro-Almagro, F., Smith, S.M., Woolrich, M.W., 2018. Discovering dynamic brain networks from big data in rest and task. *NeuroImage, Brain Connectivity Dynamics* 180, 646–656. <https://doi.org/10.1016/j.neuroimage.2017.06.077>
- Wang, X.-J., Krystal, J.H., 2014. Computational psychiatry. *Neuron* 84, 638–654. <https://doi.org/10.1016/j.neuron.2014.10.018>
- Ward, J., Lyall, L.M., Bethlehem, R.A.I., Ferguson, A., Strawbridge, R.J., Lyall, D.M., Cullen, B., Graham, N., Johnston, K.J.A., Bailey, M.E.S., Murray, G.K., Smith, D.J., 2019. Novel genome-wide associations for anhedonia, genetic correlation with psychiatric disorders, and polygenic association with brain structure. *Transl. Psychiatry* 9, 327. <https://doi.org/10.1038/s41398-019-0635-y>
- Westeneng, H.-J., Debray, T.P.A., Visser, A.E., van Eijk, R.P.A., Rooney, J.P.K., Calvo, A., Martin, S., McDermott, C.J., Thompson, A.G., Pinto, S., Kobeleva, X., Rosenbohm, A., Stubendorff, B., Sommer, H., Middelkoop, B.M., Dekker, A.M., van Vugt, J.J.F.A., van Rheenen, W., Vajda, A., Heverin, M., Kazoka, M., Hollinger, H., Gromicho, M., Körner, S., Ringer, T.M., Rödiger, A., Gunkel, A., Shaw, C.E., Bredenoord, A.L., van Es, M.A., Corcia, P., Couratier, P., Weber, M., Grosskreutz, J., Ludolph, A.C., Petri, S., de Carvalho, M., Van Damme, P., Talbot, K., Turner, M.R., Shaw, P.J., Al-Chalabi, A., Chiò, A., Hardiman, O., Moons, K.G.M., Veldink, J.H., van den Berg, L.H., 2018. Prognosis for patients with amyotrophic lateral sclerosis: development and validation of a personalised prediction model. *Lancet Neurol.* 17, 423–433. [https://doi.org/10.1016/S1474-4422\(18\)30089-9](https://doi.org/10.1016/S1474-4422(18)30089-9)
- Wickenberg-Bolin, U., Göransson, H., Fryknäs, M., Gustafsson, M.G., Isaksson, A., 2006. Improved variance estimation of classification performance via reduction of bias caused by small sample size. *BMC Bioinformatics* 7, 127. <https://doi.org/10.1186/1471-2105-7-127>
- Wilson, R.C., Collins, A.G., 2019. Ten simple rules for the computational modeling of behavioral data. *eLife* 8, e49547. <https://doi.org/10.7554/eLife.49547>
- Woo, C.-W., Chang, L.J., Lindquist, M.A., Wager, T.D., 2017. Building better biomarkers: brain models in translational neuroimaging. *Nat. Neurosci.* 20, 365–377.

- <https://doi.org/10.1038/nn.4478>
- Woolrich, M.W., Stephan, K.E., 2013. Biophysical network models and the human connectome. *NeuroImage, Mapping the Connectome* 80, 330–338.
<https://doi.org/10.1016/j.neuroimage.2013.03.059>
- Worsley, K.J., Evans, A.C., Marrett, S., Neelin, P., 1992. A three-dimensional statistical analysis for CBF activation studies in human brain. *J. Cereb. Blood Flow Metab. Off. J. Int. Soc. Cereb. Blood Flow Metab.* 12, 900–918.
<https://doi.org/10.1038/jcbfm.1992.127>
- Worsley, K.J., Marrett, S., Neelin, P., Vandal, A.C., Friston, K.J., Evans, A.C., 1996. A unified statistical approach for determining significant signals in images of cerebral activation. *Hum. Brain Mapp.* 4, 58–73.
[https://doi.org/10.1002/\(SICI\)1097-0193\(1996\)4:1<58::AID-HBM4>3.0.CO;2-O](https://doi.org/10.1002/(SICI)1097-0193(1996)4:1<58::AID-HBM4>3.0.CO;2-O)
- Yamashita, A., Yahata, N., Itahashi, T., Lisi, G., Yamada, T., Ichikawa, N., Takamura, M., Yoshihara, Y., Kunimatsu, A., Okada, N., Yamagata, H., Matsuo, K., Hashimoto, R., Okada, G., Sakai, Y., Morimoto, J., Narumoto, J., Shimada, Y., Kasai, K., Kato, N., Takahashi, H., Okamoto, Y., Tanaka, S.C., Kawato, M., Yamashita, O., Imamizu, H., 2019. Harmonization of resting-state functional MRI data across multiple imaging sites via the separation of site differences into sampling bias and measurement bias. *PLOS Biol.* 17, e3000042. <https://doi.org/10.1371/journal.pbio.3000042>
- Yao, D., Guo, X., Zhao, Q., Liu, L., Cao, Q., Wang, Y., D Calhoun, V., Sun, L., Sui, J., 2018. Discriminating ADHD From Healthy Controls Using a Novel Feature Selection Method Based on Relative Importance and Ensemble Learning. *Conf. Proc. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. IEEE Eng. Med. Biol. Soc. Annu. Conf.* 2018, 4632–4635. <https://doi.org/10.1109/EMBC.2018.8513155>