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Neuroimaging Biomarkers of Psychopathology:

A Silver Bullet for Prediction, or Too Soon to Tell?

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Abstract

With advancements in neuroimaging methodology has come increased interest in identifying neural biomarkers of psychopathology. Nevertheless, there are still major pitfalls in the use of neuroimaging for predicting disease state. Many of these surround issues of replicability and transparency in neuroimaging methods. While the neuroimaging community is making strides to resolve these issues, it remains unclear whether neuroimaging can provide the degree of predictive validity needed to identify putative biomarkers. Moreover, until the validity of neuroimaging biomarkers can be reliably demonstrated, there are ethical issues regarding disease risk disclosure and any resulting treatment decisions. To advance the identification of neural biomarkers of psychopathology we suggest 1) standardization of methods reporting as suggested by leading neuroimaging societies, 2) open sharing of neuroimaging data, and 3) use of data-driven techniques more suited for prediction evaluation (e.g., machine learning).

Key words: neuroimaging, psychopathology, prediction, replication

Introduction

Since the advent of human neuroimaging methodologies, particularly magnetic resonance imaging (MRI) and functional MRI (fMRI), our understanding of the human brain in action has increased exponentially in both health and disease. Further, this has also allowed for *in vivo* measures of human brain structure and function, and the overall safety of MRI allows for individuals to undergo multiple scans without risk of radiation exposure. This technique allows researchers to

measure brain activation during task performance (functional MRI), evaluate brain structure (structural MRI and diffusion tensor imaging), and observe functional brain networks at rest (i.e., without confounds of task demands; resting state connectivity MRI; fcMRI), all of which can be leveraged as possible biomarkers of disease. The explosion of data on the human brain has led to an increase in the desire to use these measures as biomarkers of disease in psychopathology. Indeed, there has been an explosion in the literature related to neuroimaging measures as biomarkers for a variety of disease states, ranging from schizophrenia to Alzheimer's disease. A search of PubMed for "((MRI OR "magnetic resonance imaging")) AND biomarker" revealed an exponential surge in published papers over the last 30 years, as shown in Figure 1[1]. Adding terms for specific psychopathologies yielded 237 hits for schizophrenia, 275 hits for depression, 50 hits for autism, and 1290 hits for Alzheimer's.

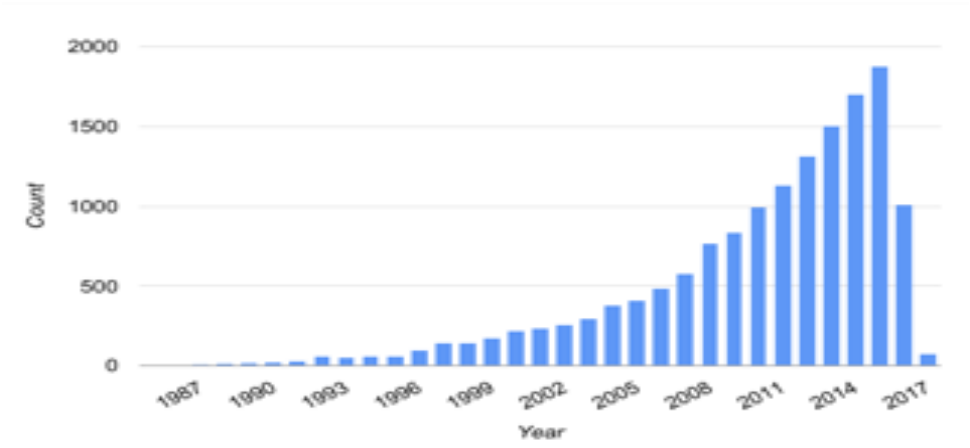

Figure 1. Number of papers per year with the terms "magnetic resonance imaging" or "MRI" and "biomarker" according to PubMed.

Furthermore, additional work is regularly being published on the topic of neuroimaging biomarkers for disease prediction, particularly as Koyama and colleagues (2016) suggest that work done strategically and longitudinally in at-risk populations stands to be quite important for early treatment and disease prevention. In addition to the search we presented above, Gabrieli and colleagues (2015) provide a review of the literature looking at brain imaging and prediction through the end of 2014. But, just in the past year, there has already been a great deal of new work looking

[1] Search was conducted on 04/06/2017, searching all fields and restricting Species to Human

at brain imaging markers and prediction in autism (e.g, Hazlett et al., 2017; Moradi, Khundrakpam, Lewis, Evans, & Tohka, 2016), Alzheimer's disease (Foley et al., 2016; Zhao et al., 2016), psychosis risk, including our own work (Bernard, Orr, & Mittal, 2017; Reniers et al., 2016), mood disorders (Drysdale et al., 2016; Wu et al., 2016), and behavioral performance more generally (Shen et al., 2017; Woo, Chang, Lindquist, & Wager, 2017). It is unlikely that work in this regard will slow down anytime soon.

Certainly, the potential to effectively predict future disease using brain imaging will remain an important area of research until the field of mental health diagnostics develops measures that compare to the differential diagnostic approaches taken in somatic disease (e.g., diabetes, cardiovascular disease, osteoporosis). However, this field is in its relative infancy, and as such, with it come major pitfalls, particularly as related to the ethics of using these measures for prediction. Specifically, the accuracy and validity of these measures remains to be seen. Here, we outline some of the methodological challenges related to human brain imaging with disease prediction in mind and we consider what this means with respect to the ethics of risk disclosure in vulnerable populations. Indeed, as recently discussed by Woo and colleagues (2017) in their review of translational neuroimaging, brain imaging as it was initially instantiated was not done to optimize methodology for this future translational and predictive focus. Further, we provide suggestions as to how future work may improve our predictive ability with brain imaging. Notably, many of these suggestions are not new to the field of human brain mapping more broadly; however, they are only just gaining traction in many cases, and are especially important to consider in the context of predictive brain imaging in disease.

Challenges in Neuroimaging and Implications for Clinical Prediction

As the reality of replication issues took hold in the field of psychological science, one important theme that was revealed was that of experimenter degrees of freedom (Simmons, Nelson, & Simonsohn, 2011). Adapted from the concept of statistical degrees of freedom, this refers to the freedom of choice in experimental design and implementation. Every element of an experiment, from whom to recruit, to the set-up of a testing room, to the order of a protocol, is subject to individual choice. Unique individual choices in experimental design and set-up may vary from laboratory to laboratory, which can influence outcomes. Such degrees of freedom, which may go unreported make experimental replication particularly challenging. In the field of neuroimaging, be it structural,

task-based functional MRI, or fcMRI, the degree of choice is even larger, further exacerbating the experimenter degrees of freedom problem. In Figure 2, we present a decision tree of potential analysis options, from choosing an analysis package, pre-processing approach, and final data analysis. Notably, this is not an exhaustive figure, as new methods are released often, and we also do not include the data acquisition parameters that also may be quite variable. In an analysis by Carp (Carp, 2012a) the author concluded that when concatenating across the analysis methods and choices available at the time of analysis, there are 34,560 ways to analyze functional MRI data, and one can come up with 6,912 unique analysis pipelines. Furthermore, he demonstrated through reanalysis of existing data, even slight changes in the analysis pipeline can indeed influence the results (Carp, 2012a). Finally, this is further confounded by issues with methods reporting in the fMRI literature (Carp, 2012b). What information is reported in a manuscript varies a great deal, and there is a general lack of standardization across journals in terms of what is the minimum level of reporting. Together, this increases the likelihood of Type I error, and makes replication especially challenging. With respect to using neuroimaging, particularly *functional* MRI for purposes of prediction and potential diagnosis in clinical populations, this is especially concerning.

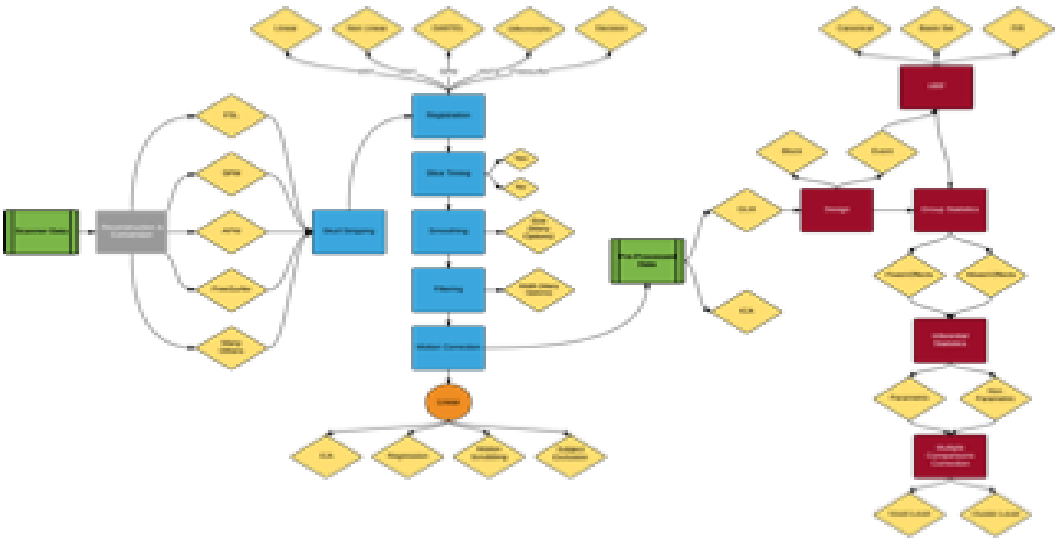

Figure 2. Decision tree of processing steps for common fMRI analysis tools. Different choices are represented in yellow, preprocessing steps are represented in blue, analysis steps are represented in red.

While the neuroimaging field has made great advances in our understanding of brain-behavior relationships, it is imperative that we are especially careful when it comes to the prediction of disease. A high rate of false positives in the broader human brain mapping literature may lead to inappropriate conclusions when relying upon functional data to predict future outcomes or to parse symptomatic individuals into diagnostic subgroups. Further, while we focused here on primarily functional MRI, similar caveats and concerns may be raised regarding fcMRI or structural imaging approaches. The processing and analysis options are many, and the details of such choices are often left behind during publication, leaving future researchers to read between the lines, potentially muddying the waters, as opposed to finding a clearer understanding of the brain in disease. Furthermore, given the pressure to publish and the high cost of neuroimaging, researchers may be tempted to try multiple statistical thresholds and/or correction methods (e.g., cluster-extent, cluster-mass, permutation) to gain a larger or more significant result. Such p-hacking has been heavily criticized in the psychological sciences, leading to a push for pre-registration of study methods. Although pre-registration of neuroimaging studies has not taken off like it has for behavioral studies, there have been calls for its use (Gorgolewski & Poldrack, 2016).

The issue of analysis degrees of freedom discussed above could be greatly reduced by following the default pipelines in one's chosen analysis package (that is, the basic suggested parameters from FSL or SPM, without deviation). However, the choice to use a default pipeline is not always free of issues. In July 2016, a paper by Eklund, Nichols, & Knutson (2016) showed that the default statistical thresholds in the most commonly used fMRI analysis packages yielded false positive rates of up to 70%. Subsequently, sensational headlines such as, "Bug in fMRI software calls 15 years of research into question[2]," and "Do You Believe in God, or Is That a Software Glitch?[3]" caused concern in the fMRI community. While packages such as FSL and AFNI have quickly addressed the concern raised by Eklund and colleagues (2016), it often takes users several years to switch/update their software. And of course, as described above, there are many choices one can make in brain imaging analysis, and defaults are not always the optimal choice given a region, network, or task of interest e.g., there is often the need to employ a smaller smoothing kernel

[2] http://www.wired.co.uk/article/fmri-bug-brain-scans-results

[3] https://www.nytimes.com/2016/08/28/opinion/sunday/do-you-believe-in-god-or-is-that-a-software-glitch.html?_r=0

for regions such as the hippocampus or the cerebellum. (A kernel smoother is a statistical technique that represents a set of irregular data points as a smooth line or surface.) Deviation from the package defaults may be necessary to most effectively answer the research question at hand. Individual research centers or lab groups may choose their own default pipelines, and these may differ greatly from the package parameters, and between groups. This further supports the need for detailed reporting of methods as highlighted above.

Suggestions for the Future: Towards Brain Imaging-Informed Prediction and Prevention

Ultimately, the question as to if we should use brain imaging measures to prognosticate diagnosis cannot be completely answered at this time. At this point, there are too many challenges with imaging methodologies themselves that are coupled with the challenges of effectively diagnosing and classifying individuals who often have heterogeneous symptoms. Thus, it is difficult to know with certainty that brain imaging will provide an effective avenue for biomarker development. With that said, we and others (e.g., Koyama et al., 2016; Woo et al., 2017) believe that this is an area of great potential and importance. There is certainly much left to be explored and better understood with respect to the brain in disease and psychopathology. Headway has been made in a variety of diseases, as summarized by Arbabshirani and colleagues (2016).

There are notable attempts at using traditional clinical diagnostic tools to predict risk for major mental illness. For example, there have been two independent attempts at introducing a risk calculator for determining the risk of conversion to major psychosis in those at a prodromal stage of the illness (Cannon et al., 2016; Fusar-Poli et al., 2017). While it remains to be demonstrated that these risk calculators have broad clinical validity, they represent significant advances in diagnostic prediction. It would be an interesting test of the utility of neuroimaging for prediction if these risk calculators were contrasted or combined with neuroimaging to test if neuroimaging adds any predictive information beyond clinical diagnostic tests.

The ethical challenges of disease risk disclosure, particularly in vulnerable populations, must also be reconciled before condoning widespread practice. Such a discussion is beyond the scope of this commentary; however, Mittal and colleagues (2015) recently reviewed the notion of disclosure of symptoms and a prodromal diagnosis in those at clinical high risk for psychosis, while Nieman and McGorry (2015) have focused on stigma associated with being at-risk for mental illness. Many

of the ethical considerations they outline (Mittal et al., 2015) apply across disease and are pertinent to the use of neuroimaging in this manner. Notably, Mittal and colleagues (2015) suggest a disclosure approach that is on a case-by-case basis, balancing the risks of added stress and stigma with the benefits of early intervention and the naming of a syndrome. With that said, imaging methods are no more definitive than current diagnostic approaches, and their use needs to be considered within this ethical context. This is particularly challenging as the heterogeneity of symptoms and disease presentation can be especially variable within a diagnostic category. Nevertheless, as the field of predictive imaging and the development of brain-based biomarkers for disease improves, the accuracy, validity, and utility of these measures will also improve making these a useful tool in diagnosis and prediction, even in these heterogeneous disease presentations. To reach this point, there are several key considerations, some of which build off the problems previously described.

First, a standardization of methods and reporting is critical for the advancement of the field of predictive neuroimaging. To create such standardization, and to publicize best practices, the Organization for Human Brain Mapping created the Committee on Best Practice in Data Analysis and Sharing (COBIDAS). This initiative resulted in the creation of standards and guidelines that were then presented to the organization for editing and input, and were ratified in 2016. The resulting COBIDAS “Best Practices” document is publicly available (Nichols et al., 2016) and is meant to serve as a guideline for all aspects of human brain imaging from data collection, processing, analysis, and data sharing. While the challenges associated with creating such a document are great (e.g., Nichols et al., 2017), so are the benefits. The field of predictive neuroimaging for disease would benefit greatly from following the suggestions as outlined by COBIDAS. An increased clarity in methods reporting and a clear statement of best practices would help prevent many of the pitfalls and the false positives outlined by Carp (2012a, 2012b). It is also imperative that journal editors and reviewers keep these in mind throughout the publication process. In a field as diverse and interdisciplinary as that of neuroimaging, particularly clinical neuroimaging, this is especially challenging.

Extending directly from this call towards standardized best practices is the notion of data sharing. One notable challenge associated with investigations in psychopathology is the recruitment of the large samples necessary, particularly to look at possible prediction. This is compounded by

heterogeneity with respect to symptoms and disease presentation. It is a commendable feat to collect data, particularly of the longitudinal sort, from 30-40 patients with psychosis as well as appropriately matched healthy controls. Yet, within this group, symptoms will vary quite a bit, as will the medication regimens for each individual. This makes reliable and reproducible prediction especially challenging. However, within the field of human brain mapping more broadly, there has been a push for increased data sharing, and openness with human brain imaging data. Such initiatives allow for data collected at different sites to be concatenated (linked together or united in a series) and analyzed by the originators of the data, but also by those with unique and perhaps transformative questions to ask. As previously noted, there can be great variability in terms of data collection, processing, and analysis parameters. However, with the sharing of large datasets, particularly when raw data is made available, researchers can use one standardized processing and analysis pipeline, and control for potential differences in scanner site and population. The result is a great increase in power, which allows for stronger investigations of the predictive validity of purported biomarkers. Further, unlike collecting large rich datasets in a small number of individuals, such large datasets include diverse heterogeneous samples, likely to be more akin to the broader population with a given disease, that may allow for the identification of disease subtypes, or patterns associated with comorbidities. While there is an important place for smaller samples with extensive individual data, it is only with larger samples that we can truly capture the diversity of the individuals impacted by a given disease or disorder, which is important for predictive validity. This approach has taken hold as seen in the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Human Connectome Project (HCP), both of which were supported by the National Institutes of Health. However, other large-scale data sets have developed more organically from the ground up as part of investigator-driven initiatives. For example, the ADHD-200 data set is comprised of eight unique data sets that were shared through the International Neuroimaging Datasharing Initiative (INDI) (Mennes, Biswal, Castellanos, & Milham, 2013). Since, there have been analysis competitions to advance our understanding of ADHD, and pre-processed data is currently available to facilitate this (Bellec et al., 2017).

The ENIGMA consortium (http://enigma.ini.usc.edu/about-2/) presents another widespread initiative aimed at better understanding a variety of disease states through the sharing of data and cross-site collaboration. Most recently, the availability of data as part of SchizConnect database (http://schizconnect.org) provides easily searchable and open access to data on schizophrenia.

However, what is still lacking, particularly for our understanding of psychosis, is openly available data during the premorbid prodromal phase of the disease. While there are large scale initiatives looking at these questions (e.g., North American Prodromal Longitudinal Study; NAPLS), to our knowledge, these data are not openly and freely accessible, particularly to researchers who may have expertise in neuroimaging big data analysis. While data from NAPLS has been previously used for prediction (e.g., Cannon et al., 2008; Mittal et al., 2010), the field would be further advanced if these data were effectively concatenated with other smaller data sets available both nationally and abroad. The open sharing of data across sites and initiatives will allow for more powerful investigations of the predictive power of neuroimaging in psychopathology and, in particular, psychosis.

Finally, from a methodological standpoint, it is important to note that more traditional analysis methods (contrast analysis with a general linear model comparing activation patterns between groups) are not optimal for this predictive neuroimaging and the development of biomarkers. While traditional imaging has provided guideposts, and laid the groundwork for more modern approaches, as noted by Woo and colleagues in their recent and timely review (2017), traditional imaging was not designed for these uses. In what they refer to as “translational neuroimaging 2.0” (Woo et al., 2017), they nicely review the existing literature, with a particular focus on work using machine learning algorithms for prediction. These algorithms allow us to use the brain itself to group individuals, as opposed to looking at extremes between groups. Indeed, advances have been made across disorders (for an extensive list and review, we refer interested readers to the excellent summary provided in Arbabshirani et al., 2017). Predictive models using these more data driven approaches certainly stand to provide key insights into brain-based biomarkers for disease that may be used for diagnosis, prediction of future disease, and prediction of treatment outcome. They also note that the development of such biomarkers may be a slow and laborious process, analogous to what is necessary in drug development (Woo et al., 2017). While we certainly agree with this machine learning approach (which could be applied to functional or structural imaging), we would be remiss if we also did not acknowledge potential challenges and limitations with this approach as well. As expertly outlined by Arbabshirani and colleagues (Arbabshirani, Plis, Sui, & Calhoun, 2017), these include issues with feature selection, overfitting of data, comparing accuracy across studies, how best to report classification results, model selection, and others. Critically, there is no one method that will provide an optimal solution for the challenges of using brain imaging metrics to predict

disease, or treatment outcomes. However, machine learning approaches currently provide the most effective methodology in this regard. We further suggest that the application of such methodologies should be done in such a way as to increase methodological transparency. This is consistent with the COBIDAS guidelines, meant to limit false positives (e.g., Carp 2012a, 2012b), a particularly concerning ethical consideration in the disclosure of psychopathology.

Conclusions

As neuroimaging methods advance (both in terms of acquisition and analysis), so too does the potential for developing neural biomarkers of psychopathology. However, as outlined above, there are several analytical and ethical issues to consider. First, neuroimaging methods must be reported in manuscripts in a way that is transparent and detailed enough to allow for reproducibility. Second, clinicians and researchers must approach disclosure of disease risk/state stemming from predictive analyses with the utmost caution. Furthermore, the development of predictive biomarkers will benefit greatly from established databases (e.g., HCP, NKI-Rockland, INDI, etc.) as well as increased sharing of neuroimaging data. In conjunction with these methodological challenges with respect to brain imaging itself, there are also other challenges. Recent pushes towards more precision medicine approaches, such as those being advanced by the RDoC (Research Domain Criteria) initiative stand to aid in the development of more refined clinical diagnostic tools. This will also help account for much of the heterogeneity seen in mental illness, and in turn will help advance the development of brain-based biomarkers. Such biomarkers have great potential to inform diagnosis and outcome prediction, but the utmost caution is required as we move forward to minimize ethical concerns from false positives and a lack of transparency.

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