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Imaging The Anxious Brain - Promise Or Hubris?

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Neuroimaging techniques have provided a unique and unprecedented insight into the functioning human brain. The emergence of functional magnetic resonance imaging (fMRI) [1] made a tool available that enabled psychiatric researchers to examine with great anatomical detail the relationship between psychological phenomena and brain physiology. Yet, twenty years later, it is important to take a step back and examine how this tool has helped to elucidate physiological and pathological anxiety related processes and to specifically address the challenges that lay ahead.

The basic premise of neuroimaging

The basic experimental approach of neuroimaging research is to define a particular process, e.g. the processing of emotions as expressed in human faces, examine the change in brain signal during this process, and – using thoughtful experimental manipulation or group comparisons - delineate a model that describes how the brain implements this particular process. However, defining a “process” is a highly heuristic endeavor and we are far from understanding the fundamental “atomic” processes that make up our cognitive and emotional experiences. Functional neuroimaging measures mass action of neural tissue when individuals process information originating from the outside world or from the inside of the body. The assumption is that greater or lesser “activation” is due to greater or lesser engagement of mass action during a specific process. Thus, greater or lesser engagement could be due to: (a) less or more efficient processing of information, i.e. more or less neural activation is needed to accomplish a process; (b) greater or lesser involvement due to “deeper” or more “extensive” or “shallower” and more “restricted” processing of the information; or (c) engagement of different brain systems in processing the information, which results in greater or lesser activation of the neural tissue under study.

Differences in activation between individuals with anxiety related problems and comparison subjects could thus be due to three fundamentally different processing types, i.e. anxious individuals could be more or less efficient in processing information, could engage deeper or shallower information processing, or could engage different types of processes, e.g. a neutral stimulus is processed as threatening due to past experiences. There is good reason to assume, and numerous experimental results that support this assumption, that all three processes play a role. Due to the fact that the presumed cognitive and emotional processes are defined heuristically, this fundamental uncertainty of the type of altered processing in individuals with anxiety related problems cannot be resolved with a single experiment. In fact, it may not be completely resolvable after multiple experiments. That is, we may fundamentally not be able to resolve which type of altered processing exists in anxiety disordered individuals due to the limited number of experiments that can be conducted and our ignorance about what the fundamental “atomic” cognitive and emotional processes are.

Where does this leave us? There are fundamentally two different directions one can take neuroimaging. First, one can develop a program of research aimed at constraining most efficiently the number of competing process theories by developing appropriate

experimental approaches to resolve the potential processing differences between anxiety disorder individuals and comparison subjects. This approach is akin to that of experimental psychology, which aims at a more precise description of the fundamental psychological processes using ingenious experimental designs and quantitative psychological theories. Second, one can – for the moment – abandon trying to resolve the precise processing differences between anxiety disordered individuals and comparison subjects and utilize the differences observed in neuroimaging experiments for clinically useful purposes. This approach, although intellectually less “deep”, may provide more practical applications for neuroimaging in psychiatry. In short, one can aim to develop neuroimaging to be a biological marker to determine diagnostic, treatment, or outcome differences.

However, there are major obstacles to this approach. Historically, there are currently no biological markers for psychiatric disorders even more than 50 years after the rise of biological psychiatry. Second, most studies that are currently presented are not aimed to examine whether neuroimaging can be used as a biological marker for a particular disorder. Instead, neuroimaging studies focus on the ability to show differences in neural activation due to specific processing of information across groups not within an individual. Third, the characteristics of fMRI, i.e. changing blood flow as a function of energetic demand in parts of the brain, and signal to noise characteristics of fMRI, i.e. the influence of thermal, physical, and physiological noise on the signal, may be such that fMRI may not be usable as a biological marker on an individual basis. Despite these obstacles, it is necessary to develop a research program that can answer the fundamental question – even if in the negative – whether fMRI can be a useful biological marker for anxiety disorders.

Can neuroimaging be developed as a test?

A central aspect of a clinical test is that it provides useful information about an individual. For example, measuring hemoglobin and comparing the obtained value to a standard enables one to diagnose with greater certainty whether an individual suffers from anemia. In particular, using hemoglobin as a biological marker one would not be interested in whether a group of anemic individuals have lower hemoglobin values than non-anemic individuals (they certainly would) but whether a particular patient has anemia or not. In short, levels of hemoglobin can be used to predict the presence or absence of a condition. Thus, the development of a clinical test poses significantly different demands on characteristics of the measure under consideration.

An important concern in psychiatry is the non-trivial problem of defining the presence or absence of a condition and whether – even if defined via standardized criteria – the condition corresponds to a distinct brain state. However, it is important to point out that presence or absence is not limited to diagnostic status, it may also relate to other clinically important conditions, e.g. response to treatment as defined by reduction in symptoms or improvement of daily functioning, engagement in social activities as measured by time spend with others, or subjective well-being as measured by ecological momentary assessments over time. Obviously, the categorical distinction between the presence or absence of a condition requires thoughtful a-priori considerations. However, one can also define categories a-posteriori derived from a continuous measure to determine what the optimal test characteristics could be.

In clinical practice it is essential to know how a particular test result predicts the risk of a condition, i.e. does a particular person have the condition when he/she has a positive test result. Likelihood ratios are a unique approach to calculate the probability of the condition, while adapting for varying prior probabilities, i.e. the chance of having a condition at the outset. *Positive Likelihood Ratio* (PLR) is the ratio of the proportion of patients who have

the target condition and test positive to the proportion of patients without the target condition who also test positive. *Negative Likelihood Ratio* (NLR) is the ratio of the proportion of patients who have the target condition who test negative to the proportion of patients without the target condition who also test negative. For example, a PLR > 10 may rule in diseases with a pre-test probability between 30% and 70%, i.e. when one is clinically uncertain. In comparison, a NLR of < 0.1 may rule out diseases with this pre-test probability. These test characteristics can be easily used in a graphical interface, e.g. the Fagan Nomogram, such that the clinician can calculate the approximate probability of an individual having a pathological condition with a positive/negative test result [2].

These statistical approaches have been applied only recently in psychiatry in general [3] and to functional neuroimaging in particular [4]. There are several advantages of the likelihood ratio approach: (1) one can obtain statistical estimates of the confidence intervals of the positive and negative likelihood ratio, which enables one to determine how good or bad a particular fMRI paradigm functions as a clinical test. (2) The resulting statistics can be practically applied to other populations and future measurements given the same fMRI paradigms and analysis pathway. (3) The statistics are comparable across different experimental approaches, which enable one to directly compare the test characteristics of fMRI with that of other clinical tests, e.g. self- or clinician rating scales.

The traditional approach to quantify neuroimaging results has been based on the application of the general linear model [5] in conjunction with predefined independent variables that characterize the particular experimental design [6]. However, other statistical approaches may provide more powerful means of obtaining neural activation patterns that differentiate individuals and can be candidate measures for the development of fMRI as a clinical test. Among these are approaches that attempt to identify signals based on the source separation problem such as independent component analysis [7], measures of temporal cross-correlations in fMRI signals across the brain such as functional connectivity [8] or measures of brain networks [9], and statistical approaches to optimally and quantitatively separate individuals activation patterns based on support vector machines [10]. These techniques will require close collaboration between statistical experts, neuroimagers, and clinical researchers to arrive at testing procedures that can truly move the field forward.

The humble advances of neuroimaging in anxiety

We have witnessed a meteoric rise of functional neuroimaging research in psychiatry over the past 15 years. The enthusiasm with which fMRI was received by the psychiatric community is understandable given its enormous appeal of examining the functioning of the “living brain”. However, stepping back one has to critically question what has been accomplished to deepen our understanding of anxiety and depression or provide novel measures to predict clinically relevant outcomes. As summarized comprehensively in a number of recent reviews [11], individuals with anxiety disorders show differences in activation of a particular set of neural substrates, which include the amygdala, the medial prefrontal cortex, and the insula. In general, anxious individuals show more activation in areas that are associated with processing emotional content and less activation in areas that are thought to contribute to top-down attenuation of bottom up, associative emotional processes [12]. Moreover, individuals with anxiety disorders show a set of brain imaging abnormalities that may be thought of as having problems with appropriately deploying processing resources that assure optimal task performance. For example, these individuals show a bias towards threat and negative emotional stimuli [13], an inability to regulate aversive emotions [14], increased self-critical assessment [15], and augmented anticipation of aversive stimuli [16]. Finally, some findings suggest severity-related neuroimaging

abnormalities i.e. greater amount of activation, can be correlated with anxiety symptoms at time of assessment.

However, we still do not know answers to some basic questions that we may hope to address using fMRI in individuals with anxiety disorders. First, there is no general account of what brain processing may causally contribute to the establishing of anxiety disorders. For example, is there a universal mechanism that results in the development of anxiety disorders, or is there a minimal set of processes that when they occur together produce clinically significant anxiety? Second, we do not know the discriminative ability of fMRI, i.e. the degree to which differences in neural activation pattern can be related to different types of anxiety disorders. Third, it is a wide open question whether neuroimaging can function as a test for individuals with anxiety disorders. In particular, can brain activation be used to make clinically meaningful predictions, e.g. diagnosis, treatment response, outcomes? Is neuroimaging useful to inform the development of new treatment approaches? Taken together, neuroimaging techniques have played a critical role in linking psychological functions to brain physiology. However, these techniques have not contributed so far to improve diagnoses or treatment of anxiety disorders. This is clearly the charge and challenge for the next decades.

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