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NEWS AND COMMENTARY

Neuroimaging and Clinical Trials

Neuroimaging as endpoints in clinical trials: Are we there yet? Perspective from the first Provence workshop

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Neuroimaging can now reveal an extraordinary amount of information about the structural, functional and biochemical characteristics of the human brain. Further understanding the biological processes underlying brain dysfunction, and how these adapt to treatment, is clearly of significance to researchers involved in medical trials. But how clinically meaningful is this information? A critical evaluation from conceptual and empirical perspectives was the goal of the first 'Neuroimaging as Endpoints in Clinical Trials' provence workshop, run from 2 June to 5 June 2010 in the charming village of Sernhac, France. Several thought-provoking, interlinked and recurring themes emerged and are enumerated here to further advance a fast developing field.

Demonstrate clinical relevance and enhance trial feasibility

Patients and clinicians are generally interested in ameliorating pain, improving cognition, protecting functional independence and raising quality of life, generally accepted as primary outcomes in randomized clinical trials (RCTs). What then could motivate the search for replacing these with neuroimage-based measures? One reason is that it may make RCTs more efficient.[1] If an intervention leads to only a modest clinical effect size, but yields a stronger neuroimage-based effect, then investigators could make do with fewer patients for the same power, or gain power for the same sample size. This in turn could enhance the feasibility and economics of a proposed trial. However, for the feasibility argument to hold, change on any neuroimage-based endpoint must correlate with change on the gold-standard clinical outcome.

In the area of Alzheimer's disease, automated processes for characterizing longitudinal changes in brain volume are emerging as potentially useful magnetic resonance imaging-based endpoints. Using data from the Alzheimer's disease neuroimaging initiative, 45 Alzheimer's disease patients were forecast as sufficient per arm of a clinical trial geared to detect a 25% relative decrease in rate of entorhinal atrophy, compared with 226 per arm based on the clinical dementia rating scale.[2] However, these estimates are based on natural history and so need corroboration under clinical trial conditions.

Dissect clinical phenotypes and improve patient homogeneity

Individual differences in patient responses to treatment are the rule rather than an exception. The assumption of a homogenous sample of patients is grounded on clinical criteria, yet in practice we often start with a mix of underlying brain pathologies that happen to resemble one another superficially. Neuroimaging may therefore help disambiguate so-called endophenotypes. Recent approaches that combine volumetric magnetic resonance imaging and genome-wide association studies are a start. For example, the *GRIN2B* gene that encodes for the *N*-methyl-D-aspartate glutamate (GLu) NR2B receptor subunit is linked to temporal lobe atrophy differences in older individuals, each risk allele associated with a 1.5% volumetric reduction.[3] Enrichment and more selective exclusion of patients based on volumetric genome-wide association studies information may help pull out signal from noise.

Improve efficiency of signal detection in drug discovery

When armed with a detailed neurobiological understanding of a specific clinical feature, functional neuroimaging can help in the selection of candidate compounds, and makes single-dose studies feasible, together helping to shorten the discovery period.[4] However, this strategy can also yield surprises. H_2O PET imaging can identify a specific metabolic change in the medial temporal lobe that correlates with clinical improvement in anxiety-disordered individuals following selective serotonin-reuptake inhibitor treatment. When the novel NK1 antagonist GR205171 was tested in comparison, it produced milder changes, and only on one side of the brain. GR205171 was therefore initially interpreted as inferior to the current gold standard; yet subsequent re-analysis identified an unequal number of individuals in the placebo group with a serotonin pathway-related genetic-risk variant that can affect image signal.[5] Interpreting neuroimaging endpoints in clinical trials may therefore require a better understanding of gene, disease and environmental interactions.

Strive for patient-specific prediction

Arguably, the most powerful reason for using neuroimage-based outcomes is the chance to identify biological signals that precede and predict clinical change.[6] J-resolved proton-magnetic resonance spectroscopy is an exciting development in this direction that allows measurement of GLu and glutamine (GLn). Relative levels of GLn and GLu ratio are linked to synaptic activity in animal studies and are abnormally regulated in mood disorders. A recent trial of riluzole in bipolar patients, a glutamatergic modulator typically used in amyotrophic lateral sclerosis, found not only evidence of a novel antidepressant mode of function, but that GLn/GLu elevation occurred before clinical response.[7] Magnetic resonance spectroscopy visible GLn/GLu is therefore of intense future interest as a biological 'leading indicator'.

Identifying personalized structural brain change trajectories is also vital, particularly for degenerative disorders. At baseline, individuals may be at different stages of a long-term disease process despite the appearance of clinical similitude. Multiple imaging baselines may therefore help to distinguish between those preclinical individuals with a rapidly developing versus quiescent degenerative process, likely to respond quite different to the same intervention.

Reduce statistical variance and boost power

A bottom line of sorts for any proposed neuroimage-based outcome is that the resultant effect size must resemble or even exceed those based on standard clinical measures. Logically, this may derive from detection of a stronger biological response, or using tools with less variance. Variance in this context can be decomposed into intrinsic physiological variance, measurement error and systematic error or bias. When neuroimaging is used for the purpose of aiding diagnosis, sensitive detection of disease burden is essential. However, when the purpose is assessing treatment-related effects such as in RCTs, then reduction of measurement error becomes a primary concern. Interesting preliminary data about a novel 'multi-atlas' strategy for processing longitudinal structural magnetic resonance images that helps minimize measurement and systematic variance was discussed; approaches such as this may help hone in on the precious parameter of interest, physiological variance, in turn leading to enhanced power in clinical trials.

Combine imaging modalities using graph-based networks

A convergence of (positive or negative) neuroimage outcomes across modalities is an important way of ensuring that observed changes are biologically meaningful. Yet methods for integrating data have until recently been highly simplistic. Graph-based measures of brain connectivity may help provide a common language, by modeling any distributed cerebral property as a graph of N nodes connected by M edges.[8] Nodes correspond to different brain regions and edges to dependencies between nodes, such as correlations between functional magnetic resonance imaging time courses, cortical thickness measures or diffusion imaging-based measurements. This is an exciting analytical strategy that attempts to move beyond the conventional view of the brain as a collection of separate data points, and is only beginning to be applied in the context of clinical trials.

Overcome data pipeline dependence

Perhaps the greatest technical challenge for the use of neuroimage-based outcomes in clinical trials is their dependence on highly specified 'data pipelines'. If for example we were to test a new anti-depressant in a RCT, we expect that alternate choices between clinical outcome measures lead to the same fundamental inferences. Or if a patient group were to deteriorate based on a clinical scale, we could not ultimately blame the instrument rather than the intervention. Unfortunately, for many of the neuroimage modalities, these simple expectations are not met. In a recent illustration, the putative effect of behavioral training on regional brain volume was found to be highly dependent on the choice of co-registration method and software package.[9] In-house pipeline development may be advantageous for discovery and basic science, but this is clearly not appropriate in the context of RCTs. If neuroimaging data are to be used in clinical trials as a primary outcome, effects should be insensitive to basic analytical and technical permutations.

Maintain trial integrity

A related challenge comes with making clear and specific *a priori* predictions. Sometimes the direction and nature of an anticipated effect are straightforward, but there can be surprises. Fox *et al.*[10] used change in whole-brain volume as one of two primary outcome measures in a beta-amyloid immunization trial of Alzheimer's disease patients. Against all expectations, the treated group experienced significantly greater volumetric loss than the placebo group (by a factor of 1.5), but rather than declare the trial clinically negative, a number of alternate explanations were considered. The over-arching risk for neuroimage-based endpoints is hence a flexibility to reinterpret null or negative findings. At the workshop there was a clear consensus that if a neuroimage-based measure is to be used as a primary outcome, then this must allow for the unambiguous interpretation of a trial's findings.

Conflict of interest

EM-P is an employee of GlaxoSmithKline.

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