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How to investigate neuro-biochemical relationships on a regional level in humans? Methodological considerations for combining functional with biochemical imaging

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HIGHLIGHTS

- Provide an overview of factors to consider when planning multi-modal imaging studies.
- Discuss technical and methodological issues for hypothesis generation.
- Discuss issues of specificity that arise in multi-modal imaging.

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ABSTRACT

There is an increasing interest in combining different imaging modalities to investigate the relationship between neural and biochemical activity. More specifically, imaging techniques like MRS and PET that allow for biochemical measurement are combined with techniques like fMRI and EEG that measure neural activity in different states. Such combination of neural and biochemical measures raises not only technical issues, such as merging the different data sets, but also several methodological issues. These methodological issues – ranging from hypothesis generation and hypothesis-guided use of technical facilities to target measures and experimental measures – are the focus of this paper. We discuss the various methodological problems and issues raised by the combination of different imaging methodologies in order to investigate neuro-biochemical relationships on a regional level in humans. For example, the choice of transmitter and scan type is discussed, along with approaches to allow the establishment of particular specificities (such as regional or biochemical) to in turn make results fully interpretable. An algorithm that can be used as a form of checklist for designing such multimodal studies is presented. The paper concludes that while several methodological and technical caveats needs to be overcome and addressed, multimodal imaging of the neuro-biochemical relationship provides an important tool to better understand the physiological mechanisms of the human brain.

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1. Introduction

The introduction of functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) made it possible to visualize neural activity changes during particular tasks or stimuli. This allowed us to begin investigating the spatial patterns of neural activity at the level of the whole brain (i.e., in terms of regions and networks), complementing the already existing and more temporally oriented technique of electroencephalography (EEG). While initially stimulus- and task-related activity were the focus of fMRI in particular, more recently the neural networks delineated during the brain's resting state have also gained a lot of attention.

In addition to the studies identifying regions and networks associated with particular functions, the question of the physiological mechanisms underlying fMRI and PET were raised in the literature early on. Ground breaking work by Logothetis and colleagues (Logothetis, 2008; Logothetis et al., 2001) revealed that the BOLD (blood oxygen level dependent) effect that is measured in fMRI is based mainly on processes related to input signals to neurons (and processing within neurons), rather than on the cellular spiking of their output signalling. As the understanding of neural inputs and processing is closely linked to questions of excitation-inhibition balance (EIB), understanding the relationship of the fMRI signal to γ-aminobutyric acid (GABA) and glutamate neurotransmission is important. An extensive literature of animal-based research along these lines now exists (see for instance Lauritzen et al., 2012), complemented more recently by work in humans that has combined fMRI with magnetic resonance spectroscopy (MRS) and receptor-based PET (Donahue et al., 2010; Duncan et al., 2011; Muthukumaraswamy et al., 2009, 2012; Northoff et al., 2007).

The MRS imaging technique allows the measurement of GABA and glutamate levels, the central biochemical constituents of the EIB, in vivo in humans. PET allows one to measure the density and affinity of particular receptors in the brain, including, amongst others, $GABA_A$ receptors (Odano et al., 2009). Hence, combining fMRI with MRS or PET opens up the possibility of directly linking neural activity changes to biochemical mechanisms. This by itself is very appealing as it helps us to understand the exact physiological basis of the fMRI signal, and is also highly relevant to investigations of psychiatric disorders like depression and schizophrenia (Brambilla et al., 2003; Jones and Rabiner, 2012; Savitz and Drevets, 2013).

However, although a promising research direction, the combined use of neural and biochemical measures on a regional level raises several methodological issues: What are the rationales for combining neural and biochemical measures? How shall we form hypotheses and design experimental paradigms that properly link neural and biochemical levels of neural activity? How shall we combine neural and biochemical measures? Why is it useful to combine them and what can they tell us; and, even more importantly, what can they not? The aim of the present paper is thus to begin describing a methodological strategy for combining neural and biochemical measures of neural activity on a regional level in humans. The focus will not be so much on technical details of combining different imaging modalities, nor on the precise details of the underlying physiology (such as the BOLD effect), but rather on devising an overall algorithm that may assist those seeking to combine neural and biochemical measures through the use of imaging techniques such as fMRI, MRS and PET. As the paper makes no claims to being an encompassing overview, references to reviews of particular topics shall be given where relevant.

2. The development of a combined neuro-biochemical experimental paradigm

2.1. Generation of hypotheses

The aim of a study is generally to test a specific neuro-biochemical hypothesis. At present there is only a limited amount of data from humans on the biochemical underpinnings of specific neural activity at a regional level on which to build hypotheses, meaning that these must be informed by the extensive animal literature available. This is a powerful approach that is arguably under-exploited in human imaging (see Alcaro et al., 2010; Hayes and Northoff, 2011, 2012, for examples of a cross-species synthesis). Use of animal-based literature in the formation of hypotheses has the additional advantage of allowing access to information at a far finer scale than is possible with humans, down to the level of single cells. Care must be taken, however, in drawing equivalences between particular brain regions in humans and non-human animals to ensure that functions do indeed overlap to the required degree.

Another rich source of information for devising neuro-biochemical hypotheses at the regional level in humans is the literature on psychiatric disorders. Known structural, functional and biochemical alterations in such conditions, especially where these can be linked to behavioural changes, provide key starting points for deducing the systems involved in particular processes in neurotypical brains. For example, known functional changes in the perigenual anterior cingulate cortex (pgACC) in depression (Alcaro et al., 2010) can be linked to the behavioural symptoms of this condition (Northoff et al., 2011), along with alterations in glutamate levels in the same region (Hasler et al., 2007) and the anti-depressant effects of glutamatergic agents (Hasler and Northoff, 2011; Sanacora et al., 2012) to build hypotheses regarding the role of glutamate in this region that can then be tested.

Relatedly, known interactions between particular transmitter-related genes and brain function in health and disease can provide a valuable starting point in hypothesis generation. A particularly well studied example of this is the serotonergic system, where many depression-related studies have been carried out (Canli and Lesch, 2007; Northoff, 2013). Findings such as a link between variations in the serotonin transporter gene, anxiety-related personality traits, and structural–functional changes in the amygdala (Scharinger et al., 2011) combined suggest themselves to studies that use multimodal imaging to more directly investigate the effect of serotonergic properties in this region, as measured with PET, on functional responses. It should be noted however that the literature relating genetic variations with particular phenotypes, be they behavioural or neural, is not without controversy and so care must be taken when building hypotheses on such results (Canli and Lesch, 2007; Flint and Munafò, 2007).

As well as a strictly hypothesis-driven approach, exploratory studies can be useful when properly informed by background literature. This may be especially true in the case of neuro-biochemical relationships in humans, where only a modest amount of work has been done to date on which to build hypotheses. Where exploratory analyses are carried out, however, they should be clearly labelled