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BRIEF REPORT

MEASURING BRAIN ACTIVITY CORRELATES OF BEHAVIOR: A METHODOLOGICAL OVERVIEW

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In the past several years, the *Journal of the Experimental Analysis of Behavior* has published two highly visible target articles that generated much interest among behaviorally-oriented researchers. The first, Horne and Lowe (1996), proposed that equivalence classes depended upon typically unobserved (and perhaps unobservable) behavior which they termed *naming*. Their proposal prompted some 30 commentaries debating its merits, including two from our research group (McIlvane & Dube, 1996; Stromer et al., 1996). The second article, by Donahoe, Palmer, and Burgos (1997), revisited the issue of whether operant behavior is always under stimulus control, even when the controlling stimuli are undetected (or detectable via a purely behavioral analysis). This article also occasioned numerous commentaries, including one from our group (McIlvane & Dube, 1997).

One might think that behavioral processes not readily detectable by behavior analytic methods would be of limited interest to *JEAB* readers, yet the nature and intensity of the response suggests the contrary. Indeed, Skinner wrote extensively about these "private events" (e.g., in *About Behaviorism* [1974]); in fact, interest in them is one factor that differentiates radical and methodological behaviorism. Moreover, in his 1989 presidential address to the American Psychological Association, Skinner suggested that a full account of behavior necessarily would entail study of unobservables. He wrote:

> There are two unavoidable gaps in any behavioral account: one between the stimulating action of the environment and the response of the organism and one between consequences and the resulting change in behavior. Only brain science can fill those gaps. In doing so, it completes the account; it does not give a different account of the same thing (p. 18).

Thus, Skinner issued an implicit long-term challenge to behavior analysts: to work jointly with brain scientists to develop a complete account of behavior. Such cooperative projects have been ongoing for many years in nonhuman animal experimentation. Where human behavior is concerned, however, collaborations between behavior analysts and psychobiologists have not yet flourished. This is unfortunate in light of rapid advances enabling the detection of brain activity correlates of behavior. Indeed, the interface of cognitive psychology and imaging has spawned the burgeoning field of cognitive neuroscience (Gazzaniga, 1995).

We suggest that it is high time for behavior analysts to become active participants in behavioral and cognitive neuroscience research. In advocating collaborations of this sort, we note an interesting historical parallel. The EAHB SIG and the *EAHB Bulletin* were founded more than 15 years ago to cultivate interest in experimental analysis of human behavior, a field that had been hitherto relatively neglected by behavior analysts; that mission has now been accomplished. Our intent here is to offer similar encouragement to behavior analysts interested in responding to Skinner's implicit challenge in the domain of functional brain imaging.

The present article was prepared as a service to EAHB SIG members who know little or nothing about current approaches to studying brain activity correlates of behavior. Our goals are to (1) acquaint such readers with current methods for detecting brain activity correlates of behavior and (2) suggest examples of scientific opportunities for collaborative research with brain scientists. We supplement this brief introduction with a list of potentially informative websites (see page XX; superscripted numerals throughout the text indicate specific sites within the list[1]) and with selected references to the cognitive neuroscience literature for readers who are interested in further study.

Electroencephalography (EEG) and Event-Related Potentials (ERPs)

EEG, a measure of electrical activity of the brain, is accomplished by placing electrodes on the

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scalp at various landmarks and recording greatly amplified brain signals. In research as well as clinical applications, EEG has been correlated with verbal and nonverbal indicators of body state. For example, alpha activity (7-12 Hz) indicates a relaxed state, whereas beta activity (13-30 Hz) indicates alertness. Power spectral analysis (PSA), which examines specific frequency bands (e.g., alpha, beta, delta), has demonstrated differences between clinical and nonclinical populations. For example, in studies with mentally retarded children, PSA has established correlations between therapeutic intervention, increased alpha, and improved performance on cognitive tasks (Psatta, Goldstein & Matei, 1991).

Event-related potentials (ERPs) are the measured electrical responses correlated with specific environmental events. For example, in the "oddball" paradigm, rare stimuli (e.g., high pitched tones) are randomly embedded in a train of more frequent stimuli (e.g., low pitched tones). The EEG associated with each stimulus type is then averaged over many presentations. By doing this, a characteristic positive-going waveform peaks around 300-600 ms following stimulus presentation. This component, termed the P300 (Donchin, Karis, Bashore, Coles, & Gratton, 1986; Donchin & Coles, 1988; Iwanami, Kamijima, & Yoshizawa, 1996) is a brain correlate that verifies detection of rare stimuli.

The P300 is but one of a number of ERP components that have been correlated with specific types of stimulation. Early components tend to be sensitive to changes in the physical stimulus parameters (i.e., luminance, spatial frequency, etc, Naatanen, 1992), but later components have been related to cognitive activity. The N400, for example, is elicited when there is a violation of what has been termed "semantic expectation" (Kutas & Hillyard, 1980).

Specific examples of how the P300 and N400 paradigms are being used to address the interests of behavior analysts can be found in a companion "Research in Progress" article (DiFiore, Dube, Oross, Wilkinson, Deutsch, and McIlvane, this volume).

Magnetoencephlography (MEG)

MEG is allied to EEG in that it measures the magnetic fields that are linked to electrical fields. One advantage of focusing on MEG is that magnetic signals are not prey to the confounds of physical diffusion (e.g., by the cranium) associated with EEG signals. MEG is used to measure spontaneous brain activity, including synchronous waves in the nervous system (Joliot et al., 1994; Deutsch, 1998). One major advantage that MEG has over the imaging techniques described below is that is has excellent temporal resolution (see *Relative Advantages of Imaging Modalities, Resolution*, below), on the order of 1 ms. However, the spatial resolution is far cruder, approximately 1-3 mm at the surface of the brain, so it is not as sensitive as some other methods of localization of function. Also, spatial resolution degrades below the surface, and at the level of the diencephalon may be only a few centimeters (see *Multimodality Imaging*, below). [2, 3]

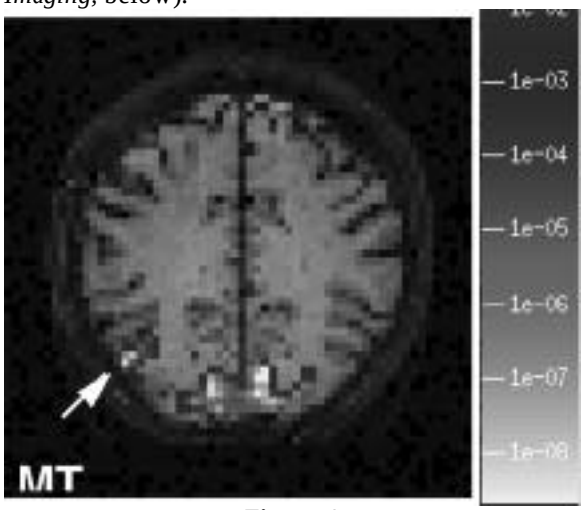

Figure 1

Positron Emission Tomography (PET)

PET provides a measure of oxygen utilization and glucose metabolism. In this technique, a radioactive positron-emitting tracer is administered, and tracer uptake by the brain is correlated with brain activity. These tracers emit gamma rays which are detected by sensors surrounding the head, resulting in a 3D map of brain activation. As soon as the tracer is taken up by the brain, the detected radioactivity occurs as a function of regional cerebral blood flow (Frackowiak, 1989), and during activation, an increase in CBF and neuronal glucose metabolism can be detected within seconds.

PET has been used widely in cognitive neuroscience over the last 15 years, and an excellent introduction to this field can be found in Drs. Michael Posner's and Marcus Raichle's *Images of the Mind* (1997). [4] Now, many of the paradigms used in earlier PET studies are being reassessed using functional MRI procedures, and these newer methods are providing yet greater flexibility to test hypotheses about brain-behavior relationships, as we describe below.

Functional Magnetic Resonance Imaging (fMRI)

MRI capitalizes on the fact that one property of atomic nuclei, their spins, can be manipulated by exposing them to a large magnetic force. While

the subject lies with his/her head in a powerful magnet (1.5 to 5 Teslas in force), a short-wave radio wave antenna varies the magnetic field in a way that is much weaker than the main magnet. The varying pulse produces a resonance signal from the nuclei that can be quantified in 3D and digitized.[5]

There has been considerable research activity in the field of perceptual psychology, with many orderly findings showing different areas of the brain "lighting up" in response to stimuli with different physical characteristics and learning histories. Even complex stimuli such as the human face have produced remarkably clear results (in fMRI [Puce et al., 1995, 1997], as well as PET [Andreasen et al., 1996]). It is noteworthy to behavior analysts that these stimuli have been used successfully in imaging studies employing matching-to-sample paradigms (in both PET [Haxby et al., 1994] and fMRI [Grady et al., 1996; Clark et al., 1997]).

A number of scientists, many of them with cognitive psychology backgrounds, have investigated attention and memory. Popular areas of study include spatial working memory (PET: Jonides et al., 1993; fMRI: McCarthy et al., 1996), working memory involving letter detection (PET: Coull et al., 1996; fMRI: Kammer et al., 1997). and sustained attention in a vigilance paradigm (PET: Coull et al., 1996; fMRI: Lewin et al., 1996).

It is possible to obtain robust, reliable patterns of activation in fMRI studies using visual perceptual paradigms, for example, mapping the processing of motion in humans to area MT (i.e., in the medial temporal lobe) (PET: Schiefer et al., 1996; fMRI: Tootell et al, 1995; Barton et al., 1996; Schiefer et al., 1996). At the Shriver Center, our interest in examining MT derives from psychophysical tests that reveal motion perception impairments in certain individuals with mental retardation (Fox & Oross, 1990). Do such individuals show the same pattern of neural activation as people who do discriminate such stimuli well? Are these apparent deficits due merely to faulty training or is there something in the individual's neurology to be considered?

Our study is inspired by a motion perception paradigm developed by Tootell and his colleagues at Massachusetts General Hospital and uses motion perception stimuli created in one of our laboratories (Oross). To activate this area, we generated a display of static dots (randomly distributed across the screen); the contrast condition displayed dots in motion that randomly jittered across the screen.

The experimental and baseline brain activation conditions are disambiguated using the "method of subtraction" in PET and fMRI. That is, an image is recorded before and after the activation task, and the former is subtracted from the latter. The results of this subtraction in our fMRI motion detection paradigm is seen in Figure 1 which indicates activation of the MT region in a single subject. The spectrum on the right represents activation level on a continuum (a *flame scale*), with red, orange, and yellow representing higher functional activity.

RELATIVE ADVANTAGES OF IMAGING MODALITIES

Resolution. In Figure 2, the spatial resolving power (y-axis) and temporal resolution (x-axis) of the various brain imaging methods described in this paper are plotted as a function of the risk of significant disruption of normal function or health of the participant (schema adapted from Churchland & Sejnowski, 1992). Autoradiography is indicated by *2-deoxyglucose.*

The new fMRI images described above are orders of magnitude more spatially and temporally resolute than PET scans (see Figure 2). Unlike PET methodology, which required extensive periods of time to capture a functional image, it was now possible to design fMRI experiments that employ blocks of trials that last mere seconds. Further, as we describe below, recent technical improvements permit the application of evoked potential-style paradigms that are even more flexible (Dale & Buckner, 1997).

PET and fMRI are indirect measures of brain activity, both of which rely on correlated metabolic measures that are presumed to reflect true activity within a region of interest. This complicates the interpretation of temporal activation, because neuronal activity may precede changes in blood flow. A more direct reflection of activity is provided by EEG and MEG. Because these techniques add far superior temporal resolution, several laboratories are now combining these techniques with fMRI to produce a more precise image of neural activity (see below).

Invasiveness and safety. MRI methods appear to be much less invasive than PET or SPECT. There is no exposure to radiation in MRI, as there is in these other procedures requiring radioactive tracers. As far as we know, exposure to the strong magnetic fields currently in use in clinical studies are without risk. That being said, there are some key considerations in recruiting subjects for MRI examinations. It is important to keep in mind that claustrophobic reactions are not rare. In our own program, we have adopted the methods of Cataldo and his colleagues at Johns Hopkins University to desensitize subjects to potentially anxiety-producing features of the scanner (Slifer et al., 1994).

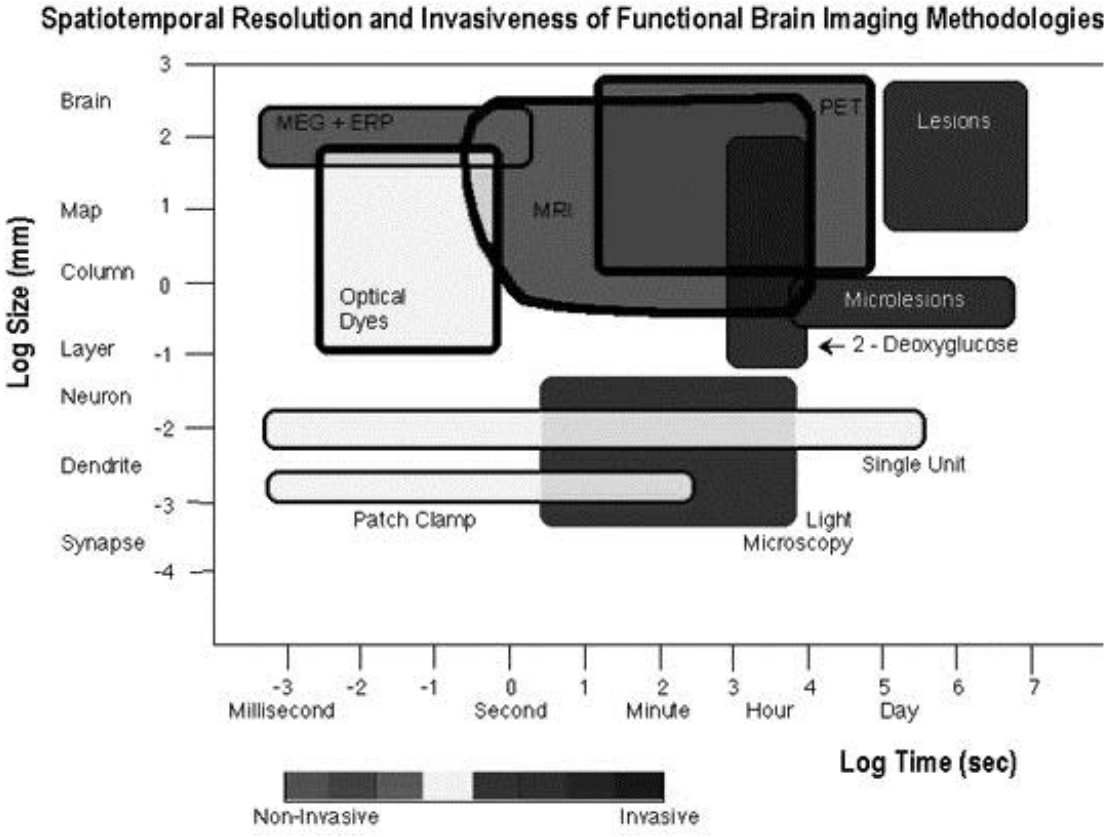

Figure 2

Expense. Another advantage of fMRI over PET is financial. Clinical MRI scans cost around $600-1200, whereas PET scans cost $1500-2000. The cost of creating and maintaining a PET laboratory far exceeds that for an MRI clinic. Structural MRI scanners are now commonplace in medical facilities in North America and Europe. Because the capital costs of transitioning from a structural MRI site to a functional imaging facility are modest compared to those for establishing a PET lab, it is not surprising to see the growing prevalence of fMRI laboratories. [6]

IMAGING OF NEUROCHEMICAL METABOLISM

Has fMRI made PET obsolete? No, because the latter technique is remarkably well suited to the visualization of certain chemical species, such as neurotransmitters. Radiolabelled tracers (*ligands*) for these transmitters can be injected and followed to specific receptor sites in the brain. This approach was used recently in an intriguing PET study of serotonin synthesis in autistic children (Chugani et al., 1997). The ability to discriminate among chemical species is not limited to PET. Magnetic resonance spectroscopy (MRS) permits detection of protons (water nuclei), phosphate compounds, lactate, and even some amino acids, within regions of interest. However, sensitivity and resolution is low for MRS, despite the chemical specificity of these images.

MULTIMODALITY IMAGING

Clearly, there are trade-offs in resolution among existing functional imaging techniques. EEG and MEG offer excellent temporal but not spatial resolution, and conversely, fMRI provides good spatial resolution but temporal limitations owing to lag times in hemodynamic changes. Why not integrate across these modalities, combining these methods' relative strengths? Investigators at the Massachusetts General Hospital have combined forces with MEG labs at Los Alamos National Laboratory and the University of Helsinki to create computational and visualization techniques that accomplish this (Belliveau et al., 1993; George et al., 1995; Dale et al., 2000).

In these innovative paradigms, the brain activation patterns imaged by EEG, MEG, and fMRI are simultaneously mapped onto a 3D structural MRI image of the brain. These complementary sources of data are synchronized in time, using the same behavioral paradigm to stimulate brain activity, so that transient changes in the evoked activity are recorded for each imaging method. By engineering a compute-intensive solution that provides the best fit of these various techniques, one can create a real-time movie of functional brain imaging. The results are remarkable: one can witness for the first time the animated spatiotemporal patterns of neuronal activity (Ahlfors et al., 1999).

CONTRIBUTION OF BEHAVIORAL ANALYSIS TO BRAIN IMAGING METHODOLOGY

At this point, the behavior analytically inclined reader may be feeling like the proverbial stranger in a strange land. To what extent will venturing further into this land advance the behavior analytic research agenda? We suggest that behavior analysts will increasingly encounter situations in which measurement and analysis of private events and their neural correlates will be attractive subject matter. As just one example, behavior analysts have been interested whether or not stimulus equivalence classes exist before the critical tests to document them (see Sidman, 1994 for a brief review of this issue). McIlvane and Dube (1990) argued that this question should be reformulated, because good behavior analysis does not generally explain behavior in terms of unobservable mental structures with some type of independent existence. Yet this question was of sufficient interest that behavior analysts posed it and attempted to answer it. The companion "Research in Progress" piece in this volume provides an illustration of how studying brain activity correlates of behavior might allow a revisitation of this research question in a manner that is more in keeping with the methods and perspectives of contemporary behavior analysis.

We also suggest that forays by behavior analysts into behavioral and cognitive neuroscience research will inevitably influence scientific theory and practice in other disciplines (cf. McIlvane, Dube, & Serna, 1996). For example, by offering techniques for experimental rather than strictly statistical control of behavioral variability, behavior analysts might help increase the yield of otherwise very expensive imaging experiments. These methodological strengths can provide rigorous experimental control for brain imaging procedures, as they develop, and perhaps assist in publicizing the contributions that behavior analysts can uniquely make for a broader scientific audience. Moreover, behavior analysis also offers well-developed research programs and procedures in a variety of areas relevant to understanding both human and nonhuman behavior, including the development and measurement of stimulus control and the quantitative analyses of reinforcement processes. It would be a pity if these behavior analytic concerns were ignored as the new science of brain imaging develops.

URLs FOR NEUROIMAGING WEBSITES

[1] Good general neuroscience references with rich links to neuroimaging sites include:

the Neuroguide:

http://www.neuroguide.com/

the WWW Virtual Library on Neurosciences:

http://neuro.med.cornell.edu/VL/

the Whole Brain Atlas:

http://www.med.harvard.edu/AANLIB/hms1.html

[2] Discussions of functional imaging using MEG with illustrations can be found at:

http://mcns10.med.nyu.edu/research/meg/meg.html

[3] Real-time movies of MEG and simultaneous MEG/EEG recording can be seen at:

http://www.ccs.fau.edu/brain_dynamics/MEG143_EEG32.html

http://www.bic.mni.mcgill.ca/demos/

[4] The history of positron emission tomography and examples of PET imaging studies are seen at:

http://www.macalester.edu/~psych/whathap/UBNRP/Imaging/pet.html

http://www.crump.ucla.edu/PBA/

[5] Links to MRI research training programs, MRI imaging WWW sites, gopher MRI sites, software, and periodicals can be found at:

http://www.fmri-world.net/

http://www.duke.edu/~richwarp/fmri.html

[6] For a summary of capital costs for these imaging technologies, see the website:

http://ecco.bsee.swin.edu.au/neuro/brainmap1/chart.html

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