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FINAL TECHNICAL REPORT

Cognition in the Brain: Investigations Using Positron Emission Tomography

Massachusetts General Hospital
Boston, MA
June 16-17, 1991

1 INTRODUCTION

The AFSOR-sponsored workshop **Cognition in the Brain: Investigations Using Positron Emission Tomography** was held on June 16 and 17, 1991 at the Massachusetts General Hospital in Boston.

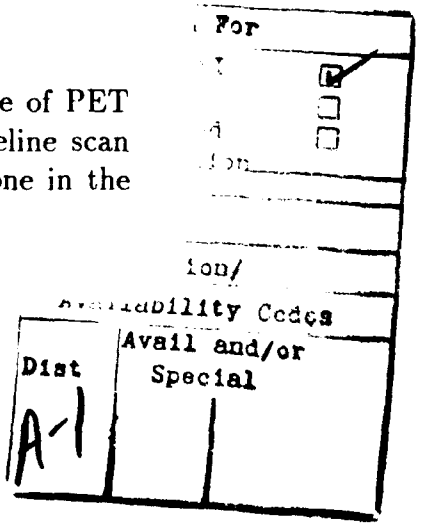
Positron Emission Tomography (PET) provides a means for localizing sites of cognitive processing within the human brain. Diverse processes involving memory, sensory perception, high level vision, and language may be studied with this methodology. Initial results have generated enthusiasm and interest at many institutions. This enthusiasm appears to be leading to a dramatic increase in the number of PET facilities and use of PET to study cognitive processes. Thus, it was deemed important to critically review the major components of the experimental technique and make recommendations about the more desirable ways of using the technique. The goal of this conference was to identify and begin a continuing discussion of the major issues affecting the generation and testing of new hypotheses about cognitive processing, and to provide some guidance for new groups of researchers; this guidance will help them not only to avoid re-inventing the wheel, but also to produce work that is immediately interpretable by the community at large and consistant with a common data-base.

The workshop covered three major topics: (1) Anatomic localization of components of cognitive processing; (2) Issues of data analysis arising from cognitive function experiments; and (3) Task design in cognitive function studies with PET. Accordingly, the meeting was organized in three sessions. Each session was of 3 hours duration, including an introduction by one or more experts to frame the discussion. There were no other formal presentations A summary of each session is presented below along with a list of participants.

2 Session 1 — ANATOMIC LOCALIZATION

Allan Evans, introduced the subject and moderated the session.

For the purpose of this discussion we can characterize the use of PET to study cognitive function as a two step process. First, a baseline scan is taken which the subject engages in everything that will be done in the



"activation" task except the component under investigation. The pattern of blood flow evoked in the baseline task is subtracted from that evoked in the experimental task due to the specific process of interest. The difference forms an image comprised of the spatial distribution of activation. (The methods for distinguishing chance findings from true activation are discussed in Session 2.) Second, foci of activation are localized by mapping the PET activation image onto a structural coordinate system. This session addressed questions regarding which structural coordinate system to use, and how to perform the mapping of function to structure in the most accurate way. One may impose the mapping of function to structure via an individual anatomic reference, and this approach leads to experimental designs that feature within subject comparisons. Alternatively, one may choose a design that emphasizes intersubject comparisons; this requires methodology for spatial normalization of studies with groups of subjects and reliance on an "average" anatomic reference scheme.

Choice of Structural Coordinate System: Two basic choices have been described for the structural substrate: (1) atlas-driven, and (2) use of a stereotaxic space. The atlas-driven approach relies on a anatomic space which labels each coordinate as belonging to identified structures (e.g. thalamus) and/or cytoarhitechtonic regions (e.g. Brodmann area 4). Examples of nonlinear atlases were discussed by Evans and by Greitz. In the stereotaxic approach gross spatial properties– shift, rotation, and scale – are normalized and standardized. The most popular stereotaxic approach was devised by Talairach and Tournoux (1967, 1988) and first applied to PET by Fox and colleagues (1985). The so-called Talairach space is based on the intercommisural line (AC-PC line) and the midsagittal plane. The spatial dimensions of an individual brain are normalized in a linear (or piecewise linear) way to a standard size. Then, one locates the activation in Talairach coordinates. The basic difference in these approaches is that use of the Talairach space does not imply an identifiable anatomic or cytoarchitechtonic structure; it merely provides a means for investigators to communicate their findings in a standard coordinate system.

Use of the Talairach space was considered most practical; although it is not without problems. One problem is the localization of the AC-PC line from PET data. Neither the AC or PC can be directly visualized in

PET scans; one must rely on visualization of structures such as the corpus callosum, or relation to the glabella–inion line. Evans estimated 2-3° errors in the angle of the AC-PC line, leading to localization errors on the order of 3-5 mm. As currently used, the Talairach mapping assumes symmetry of the two hemispheres, an assumption violated by real brains. The consequences of these problems in a given situation cannot be easily quantitated at this time, but are one of the limits to the method.

Mapping of Function to Structure: The issue of mapping to structural coordinates was discussed. Several groups have proposed unfolding (flattening) the cortical surface, thereby reducing the dimensionality from three to two dimensions. The effect of this mapping would be to increase spatial discrimination; but some difficulties may be expected. For example, random localization error would be expected to increase.

Within-subject *vs.* Intersubject Averaging: Within-subject designs eliminate anatomic and functional variability. However, it was noted that two types of functional variability have been observed and within-subject averaging only protects against intersubject variability and not against functional variability within a given subject (run-to-run variability). With single subject designs habituation and overlearning may be a more vexing problem. Another risk in such designs is that a single individual may be an outlier.

It is clear that intersubject designs must solve the problem of standardizing the individual scans. For subjects with brain lesions this approach may suffer from greater anatomic variability. In fact, studies in normal subjects by the Montreal group suggest that residual anatomic variability (after stereotaxic transformation) and functional variability are of the same order of magnitude. Studies by Evans et al have shown that nonlinear mapping for intersubject averaging gives better definition but requires an anatomic reference, such as MRI, human identification of landmarks, and increased computational burden.

Discussion and Conclusions: The basic consensus was that mapping to the Talairach space was the most practical means for intersubject averaging. To facilitate communication of results the group agreed to standardize

the origin of coordinates in Talairach space at the position of the anterior commissure on the midsagittal plane.

3 Session 2 — DATA ANALYSIS IN COGNITIVE FUNCTION STUDIES

RSJ Frackowiak, Moderator

The main goal of data analysis in cognitive function studies with PET is the detection of neurophysiological changes associated with changes in cognitive state. The major areas addressed in the discussion include

1. The use of regional cerebral blood flow (rCBF) vs integrated count (IC) data. What is gained/lost by non-linear transformation of integrated count data to rCBF images in flow units?

2. Stereotactic normalization may be viewed as a method for removing systematic anatomic variation when comparing different subjects. To what degree does stereotactic normalization permit voxel by voxel comparison of data accrued over subject groups? How much intersubject variability in gyral pattern and functional response remains after normalization?

3. The technique of global normalization — renormalizing the within-task mean blood flow to a grand mean — is widely used. What are the consequences of the assumptions inherent in this approach? What is gained?

4. What is the accuracy and precision of measurements of change by current PET methods?

5. Most experiments compare one or more cognitive states, the null hypothesis being no change. How is the analysis interpreted with respect to the null hypothesis? How can we protect against false positive when analyzing a large number of correlated voxels?

3.1 Summary

Change Distribution Analysis: The technique of "Change Distribution Analysis" (Fox, Perlmutter, Raichle, 1988) was introduced by Peter T. Fox. The main elements of change distribution analysis include:

1. Stereotactic normalization of PET scans to the proportional stereotactic space of Talairach and Tournoux (1967, 1988) in which the brain is oriented with respect to the intercommissural (AC-PC) plane and linearly rescaled to a standard size.

2. Normalization by the global mean. This step attempts to remove the variation of the run-to-run global mean which is on the order of 10%.

3. Detection of local change is accomplished by subtraction of scan pairs to produce images of 'Change Scores' that reflect the magnitude of activation. The data are reduced by a local extrema search, resulting in a location and change score for a reduced data set.

4. Assessment of significant change is accomplished by an omnibus significance test. This procedure tests the hypothesis that the distribution of change score is normal.

5. Identification of significant focal change requires a positive omnibus test. Data are transformed to Z- or t- scores and reported in rank order with their respective positions, under the assumption of spatially homogeneous error variance. No explicit correction is made for the large number of comparisons; however, the most significant changes are likely to be those with the highest Z-scores.

The question of whether integrated counts might be used as an index of blood flow in place absolute measurement of blood flow was also addressed. Fox and co-workers have shown that change distribution analysis results do not depend on measurement in absolute flow units; however, differences in global mean are not preserved. Other groups using a variety of methods confirmed this finding.

Statistical Parametric Mapping: The technique of "Statistical Parametric Mapping (SPM)" was introduced by Karl J. Friston.

SPM refers to the construction of parametric images (Friston, et al, 1991b) where, under the null hypothesis, the voxel values are distributed according to a formal statistic. The major elements of this technique include:

1. Stereotactic transformation (shift, rotation, and magnification) is performed (Friston, et al, 1989), followed by a nonlinear shape transformation (Friston, et al, 1991a).

2. Global normalization is performed by regression analysis (Friston, et al, 1990) which computes the mean activity and error variance for each voxel.

3. Image comparison is performed, voxel-by-voxel, on the mean activities for each condition using a test quotient with the t distribution to create a map of t values (SPMt), effectively an image of significance.

4. Detection of local change relies on rejecting the null hypothesis that the measured distribution of t values across the whole brain could have occurred by chance.

5. Detection of significant activation is achieved by thresholding the measured t map at a level which takes into account the number and correlation of the voxels analyzed. The threshold for multiple comparisons is based on stochastic theory, assuming the smoothed image is an uncorrelated random field which has been convolved with a Guassain filter. The probability per pixel of a false positive, Ω, occurring with threshold τ and image smoothness s is given by

$$\Omega = \frac{1}{32\pi s^2 p e^{\tau^2}}, \tag{1}$$

where p is the area under the normal distribution between τ and infinity.

The Euler Characteristic (Worsley, et al, 1991): The concept of the "Euler Characteristic (EC)" was introduced by Keith J Worsley. This approach is independent of the SPM, but is convergent in that it provides a deeper understanding of the statistical principles of image comparison. The concept of EC relates to the number of "topological islands" in a process. At high thresholds the EC tends assymptotically to the number of extrema found by the change distribution analysis and the thresholded SPM analysis. Using the EC, the threshold correction has an identical dependency on smoothness as the stochastic formulation of SPM. The probability of a false positive per pixel is given by

$$\Omega = \frac{1}{2(2\pi)^{3/2} s^2 e^{\tau^2/2}/\tau}, \tag{2}$$

a result that is similar, but more general, to the stochastic SPM theory given above.

Confounding of Global and Regional Indices: The relationship between regional and global indices of blood flow was discussed by Richard Carson. The issue of the confounding of global differences and regional estimates was illustrated using ROI analysis of rCBF maps and highlighted by findings which suggested both global difference and regional difference with the two interacting to render both insignificant. The point of this example is to question the assumption that both global and regional effects can be estimated independently. Independence can be more closely approximated by reducing ROI's to voxels.

The confounding of spatial extent and activation foci in activation studies was discussed by Henry Huang. The issue is that there remains an unsolved and perhaps unsolvable problem in analysis of activation foci when it comes to measuring spatial extent and intensity

3.2 CONCLUSIONS

Although there are several approaches to analysis of activation studies, there are areas of general agreement:

1. Integrated counts may be used as an index of rCBF and neuronal activity in the functional mapping of normal subjects. The measurement

of factors affecting the global mean require a measure with absolute scale.

2. The standard stereotactic space in which to present results is that described in the atlas of Talairach and Tournoux (1998).

3. The pixel-based methods, Change Distribution Analysis and Statistical Parametric Mapping should be standardized and cross validated. A commitment was made to make such software available to centers engaged in functional mapping.

4. The problem of mass non-independent multiple comparisons implicit in statistical parametric maps has now been addressed in terms of appropriate thresholding.

5. Pixel-based analyses are an important alternative to ROI-based approaches.

6. The distinction between a hypothesis-led study, an exploratory study and a confirmatory study (replication) should be born in mind and where appropriate, emphasized. These distinctions relate to the ever present danger of false negatives, with the criteria suggested above.

4 Session 3 — TASK DESIGN IN COGNITIVE FUNCTION STUDIES

Steven Petersen, Moderator

4.1 Introduction, Petersen

Studies involving PET and human subjects represent a limited resource with respect to the costs incurred for equipment, personnel and analysis. This gives special impetus to the careful design of experiments.

The assumptions underlying the use of PET and similar neuroimaging techniques include: (1) The notion that cognition resides within the neural substrate; (2) Functional localization is possible; and (3) Changes in cognitive

processing demands lead to changes in neuronal activity. The goal of these studies is to localize discrete functional areas which are anatomically and cytoarchitechtonically distinct. To find such areas we must search for isolable cognitive components, or sets of computations that underlie a function. Thus, our descriptions of these functional areas should focus on the processing to which that area contributes.

Stages of Experimental Design: There are three stages to the "proper" design of PET experiments: before, during and after the scanning session.

Before beginning scan sessions, be as exhaustive as possible. Specify questions in terms of basic processing levels, decomposing the components of the computation into its primary elements. Utilize information from as many disciplines as possible to understand the nature of the proposed experiment and then consider the constraints imposed by a PET imaging experimental design. Pass the proposed experiment through a group who will challenge both the underlying assumptions and the experimental design. A PET study should not be a single task pair, but rather a set of comparisons that as a package address an issue. Use more rather than fewer constraints.

While accruing scan data, vary as little as possible between the experimental and baseline tasks.

In the analysis phase, be open to the prospect that the data may suggest reanalysis. Also, be humble if the data seem controvertible; PET results remind us how little we know about neurobiology.

Justifying Subtractions: One of the most controversial areas in task design is the need to justify the subtraction of activation images as a key step in hypothesis testing. Subtraction removes the baseline processes and anatomic information that are also present in the experimental task. The problem is to justify attribution of the remainder to the cognitive process under investigation. In order to be more confident that a suitable baseline task is selected for subtraction, it was suggested that additive factors designs be used. Additive factors methodology is not the same as dissociation logic. With dissociation logic, one expects different areas to be activated by different tasks (i.e., using the same visual stimulus but the task focus is color vs. motion). A simple two task subtraction design will not always be sufficient to guarantee additive factors; rather, factorial designs may be necessary.

Task Difficulty: Can one create a second task by merely increasing the level of difficulty? Does increasing task difficulty increase CBF? Such questions can only be addressed in the light of experimental evidence. The experimental data are incomplete; but some important information is available: First, there is high correlation between spike frequency in electrical recordings at the dorsal root ganglia and glucose utilization and energy metabolism. And second, there is evidence that the increase in metabolism is associated with the terminals rather than the cell bodies. These findings are consistent with a relationship to neuronal function/activity. It should also be noted that blood flow is a different and somewhat indirect measure. Hoever, the available data show that blood flow increases rapidly, proportional to increases in glucose utilization; whereas, the increase oxygen metabolism is much smaller.

It should be remembered that measures such as reaction time and error rates are not direct measures of task difficulty. Peter Fox pointed out that factors such as attention and controlled vs. automatic processing are confounded with difficulty.

Converging Evidence: Convergent evidence from independent measurements can strengthen the task design. For example, reaction time measured during scan sessions or post-scan testing can be used as supporting evidence that the subjects were engaged in the specific task under investigation. Performing multiple subtractions, from different control states, can ascertain that the task involves specific discrete components.

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