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PET: Exploring the Myth and the Method

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New research tools such as PET can produce dramatic results. But they can also produce dramatic artifacts. Why is PET to be trusted? We examine both the rationale that justifies interpreting PET as measuring brain activity and the strategies for interpreting PET results functionally. We show that functional ascriptions with PET make important assumptions and depend critically on relating PET results to those secured through other research techniques.

1. Introduction. The multicolored images produced by PET [positron emission tomography] are extremely captivating and seem to offer a direct picture of the human brain at work. In specific tasks, brain areas differentially light up, suggesting that the most active areas are the ones responsible for producing the behavior in question. While the popular press sometimes exaggerates what researchers in fact claim, it is the dramatic character of these images and the tantalizing suggestions about brain function that together bestow credibility on PET, not just with the lay public, but with scientists engaged in PET research. This is not a bad thing. Scientists [and others] are right to be impressed when a new technology gives dramatic results, especially when the results are empirically plausible, consistent with established or developing theory, and interpretable vis-à-vis the results achieved through other techniques. As philosophers of science we are interested in how the evaluation of new technologies is carried out. Multicolored PET images are many steps removed from the phenomena themselves—the activities going on in the human brain. Each step in the production of these images involves transformations of the phenomena that allow for ar-

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tifacts. Interpretations of the results rely on assumptions; should they be false or implausible, another opportunity for artifact arises.

Our purpose for this paper is to evaluate critically the epistemic justification of PET, with the goal of better understanding both its potential and its limitations. In raising epistemic questions our goal is not to deny that PET has enriched the scientific understanding of how brains work; we firmly believe it has. Rather, we are concerned with understanding *how* it is epistemically appraised. There are two major parts of this endeavor: first, evaluating whether PET measures the brain activity associated with cognitive tasks, and second, evaluating how PET results are interpreted in terms of psychological functions. As we shall see, with respect to the first issue, PET is, by now, relatively unproblematic. It is with respect to the second issue that PET confronts the greatest epistemic challenges.

2. Establishing that PET Measures Neural Activity. Whether PET images reliably identify the neural activity of discrete brain regions depends on whether its underlying rationale is prima facie plausible and free of major epistemic problems. The rationale depends upon the following assumptions, generalizations, hypotheses, and antecedent conditions:

1. (a) The performance of any task requires certain types of information processing; (b) not all regions of the brain process all types of information; and (c) discrete regions of the brain are involved in the performance of any given task. [*assumptions*]
2. The performance of any given task alters neuronal activity, which in turn alters local blood flow and metabolism. [*empirical generalization*]
3. With a radiolabeled tracer in a subject's blood, PET can directly measure changes in local blood flow or metabolism, and indirectly measure changes in neuronal activity. [*hypothesis*]
4. Positron-emitting isotopes can be administered intravenously [or inhaled]. [*antecedent condition*]
5. The PET scanner detects gamma rays, which are a byproduct of positron-emitting isotopes. Paired gamma ray detections are computed into the functional image. [*antecedent condition*]

Since these claims, if true, suffice to show that PET does measure brain activity, we must only determine whether each step is epistemologically justified. Most of them are. For instance, (1a–c), while not accepted in *all* quarters, are nevertheless consistent with the localizationist theory of brain function that is currently the received view among neuroscientists. It is a virtue of PET that it is wedded to assumptions that are consistent with the established approach to brain function that has emerged from single-unit recordings and lesion studies. Because (2) is consistent with the neuron doctrine, for similar reasons, it too is plausible. And since positron-emitting isotopes *can* be administered intravenously [or inhaled], (4) is not controversial. Thus, if there is a problem with the PET experimental rationale, it lies with (3) or (5). Evaluating these claims, however, requires that we say something about how PET works.

For studies where the tracer is administered intravenously, the procedure runs as follows. First, subjects are given specific directions for the task they are to perform. Once a subject's head is inserted into the scanner aperture, it is immobilized. Following stabilization and alignment, subjects are instructed not to move their heads. An IV is then inserted. The subject will remain in that [rather uncomfortable] position until the end of the session.

A radioactive isotope, usually ^{15}O, having been incorporated into a saline solution, is then administered. Given its short half-life [122.3 seconds], an additional dose of ^{15}O-labeled water must be administered before each scan. Each scan lasts approximately 40 seconds. A total of 5 to 11 scans are performed during any one session. A 20-minute interval between scans allows (a) the isotope to fully dissipate and (b) the next batch tracer to be made and transported.

The reliability of PET to measure local brain activity hinges upon the process of positron annihilation and the ability of the scanner to detect gamma rays. Owing to physics, the process of positron annihilation is now relatively well understood. A positron-emitting isotope, say ^{15}O, is made in a cyclotron by accelerating protons into the nuclei of oxygen. The incorporation of an extra proton into the nucleus produces an unstable isotope. To regain stability, the proton breaks down into two particles, a *neutron* and a *positron*. The former remains with the nucleus, while the latter travels away from the site of generation. Within a short distance, the positron collides with an electron. As a result, both the positron and the electron are annihilated and two gamma rays are emitted at precisely 180° from each other. These emitted gamma rays are recorded by the scanner and an event is registered when and only when a pair of gamma ray detectors make "simultaneous" detections. With this "coincident detection" method of event recording, one can not only pinpoint the precise location of the site of gamma ray emission, one can generate an image. The resolution of current PET images ranges from 1 to 8 mm, depending on both the type of scanner and tracer used (Martin et al. 1991, 313). See Figure 1.

Because the PET scanner *does* detect gamma rays, gamma rays *are* a byproduct of positron-emitting isotopes, and paired gamma ray de-

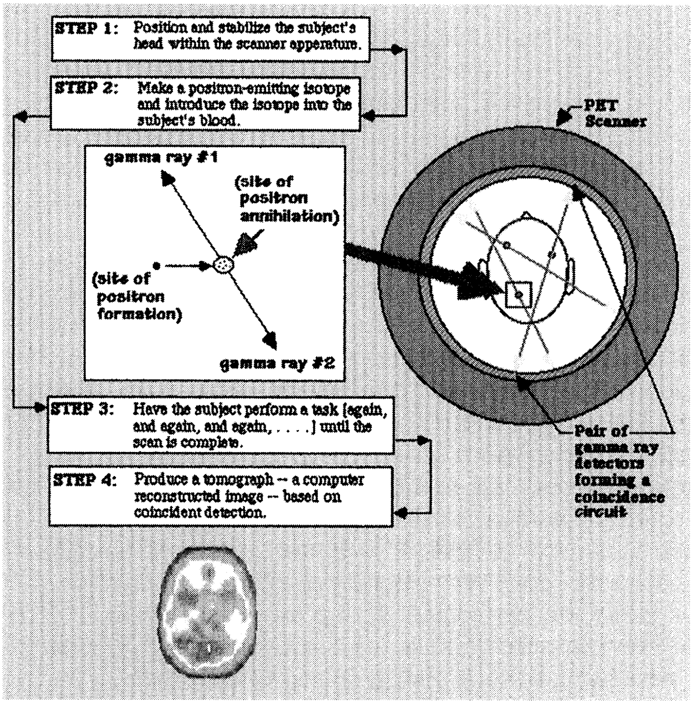

Fig. 1: Adapted from Posner & Raichle, 1994, 63.

tections *are* computed into the image, it follows that (5) is prima facie plausible. That leaves only (3).

Although the isotope *is* carried in the blood, strictly speaking, it is not local blood flow that gets imaged but, rather, the site of positron annihilation. But not only is the site of positron annihilation once removed from the site of positron formation, blood flow measurement is itself once removed from the neurons being activated. Consequently, PET's measurement of blood flow is indirect as well. Yet, since (3) can be amended without harm to the PET experimental rationale, we find it to be prima facie plausible.

But the allure of PET is not that it measures local brain activity. Rather, it is that PET is supposed to relate structure with function. We turn now to the challenge of establishing the link between structural activities and functional interpretations.

3. Do PET Images Capture Structure-Function Relations? Merely finding increased blood flow in areas of the brain during performance of a particular task does not reveal the function of that locus. Bechtel and Richardson (1993) refer to the inference from the activity of an area in the performance of a task to its being the locus of the task as *direct* or *simple* localization. These are the kind of localizations advocated by Gall and Broca in the 19th century, and are the ones that are often proposed at the outset of an inquiry. Such localizations can be useful in pointing to areas of a system involved in a task, but even then they revel nothing about *how* the task is done. Doing *that* requires decomposing the task into subtasks and localizing these in appropriate structures.

In the brain, one large area is not alone responsible for performing whole tasks, psychological or otherwise. Rather, performance is generally distributed over numerous areas, each of which does part of what is needed to perform the overall tasks. As noted by Petersen and Fiez (1993, 513), "a functional area of the brain is not a task area: there is no 'tennis forehand area' to be discovered. . . . Any task or 'function' utilizes a complex and distributed set of brain areas." Accordingly, what must be localized or mapped onto the brain through neuroimaging are "simple operations." The aim is to determine the distinctive contributions, or simple operations, performed in different regions of the brain.

The standard and potentially very powerful strategy for localizing simple operations is the *subtraction method.* A subject in a PET study normally will perform a different task during each of several scans. If tasks are chosen with clearly defined cognitive and sensorimotor components, and if they differ in just one or a few simple operations, comparisons between two scan images should isolate the component which is uniquely present in one task and absent in the second. To identify the locus of the additional operation, the image generated during performance of a *control task* is *subtracted* from the image generated during the performance of an *active task*, generating a *difference image.* One then identifies the area(s) revealed in the difference image as the locus of the additional operation. To increase the likelihood that one has identified the right locus, difference images across subjects performing the same task are averaged.

The subtraction method assumes additive, independent processes can be inserted (or deleted) separately into a cognitive operation without altering others in the process. Otherwise, the additional brain component found in the active task cannot be assumed to carry out the additional process. This assumption is not obviously true, and recent work in computational modeling, which often relies on interactive processing components, gives one reason to be suspicious of it. Although this assumption is fallible, we will suggest below that by relating PET to other techniques of cognitive neuroscience, its credibility is enhanced.

There are, however, a variety of other challenges to relating PET to cognitive function. First, as we have seen, PET scans measure blood flow over a prolonged time span, usually about 40 seconds. Many cognitive tasks, however, require only a few milliseconds. If increased activity in a functional area is too minimal, or is counterbalanced by decreased activity during other parts of the scan, PET will fail to detect it.

Second, subtraction images across subjects performing a given task are often, but not always, averaged so as to increase the signal-to-noise ratio. While this seems relatively unproblematic for primary sensory areas, anatomical variability in higher processing areas may so dilute the result that no area will show up. Given this limitation, it is remarkable that so many positive results are obtained (Posner et al., 1994, 220), perhaps indicating that philosophical worries over multiple realizability of cognitive functions are exaggerated. PET researchers contend not only that variability differences are small, but that the averaging techniques are themselves very effective (Petersen and Fiez 1993, 514).

Third, in order to employ the subtraction technique with a scanning period of 40 seconds, the same task must be repeated many times. This means that tasks must be extremely simple. Examples include passively processing visually presented lists of linguistic stimuli and generating verbs in response to visually presented nouns. Such tasks are not the kinds of cognitive tasks people perform in their usual lives: we generally read whole sentences and generate new words in the context of creating sentences. This raises the question of whether inferences about general processing capacities of parts of the brain can be drawn from atypical, ecologically very unrealistic tasks.

Finally, there is only a small pool of tested subjects over which to make functional generalizations. Accordingly, in only a very small number of these studies has it been possible to test for, say, gender-related differences (Stufflebeam 1996).

While these are all genuine concerns about the reliability of functional conclusions drawn from PET, none of them invalidates this use of PET. A much greater concern, however, does arise. PET only shows that a part of the brain is active during the performance of a particular task. It cannot give any direct indication of exactly what that part of the brain is doing. The clues about what it is doing must come from elsewhere. PET researchers often acknowledge this explicitly, as when they note that PET data makes sense only when "information from other disciplines is considered" (Fiez and Petersen 1993, 287). Although PET can be used in concert with other tools "to identify sets of brain regions involved in particular types of processing," what it cannot do—contrary to another comment of Petersen and Fiez (1993, 287–288)—is "characterize the types of computations performed by an individual region."

PET's dependence upon other techniques/disciplines is not itself a limitation. Rather, it serves to promote an interdisciplinary approach to modeling human cognitive processing, an appeal PET researchers themselves are the first to make (e.g., Petersen and Fiez 1993). Such multidisciplinary collaboration provides a measure of consistency to the results obtained. But even if PET were the only tool available, it would not follow that functional neuroimaging were bankrupt. Even if the components of cognitive processing did not perform fixed simple tasks in a serial sequential order, so that PET misidentified component tasks and how they were added together to perform more complex tasks, PET studies would generate initial working hypotheses that could then be refined as researchers recognized the failure of linear models.

4. Uses of PET to Link Structure and Function. Even with reliance on tools from other parts of cognitive neuroscience, there are challenges in securing an assignment of function to a given neural region. These challenges are specific to the sorts of collaboration that are employed. One source of collaboration is task analysis, a traditional forte of cognitive science. Such task decomposition is critical for PET since the subtractive method relies on it to determine the component tasks that are involved. Clearly, though, different task decompositions will result in different subtractions and different analyses of the subtraction results. Another source of collaboration is deficit analysis, a traditional forte of neuropsychology. But lesion studies, like PET data, are subject to multiple interpretations. They also fail to reveal directly the underlying computation. To make our analysis more concrete, we now turn to two prominent examples of PET-based attempts to link structure and function.

Lexical Processing. Since the 19th century, neuroscientists have sought structure-function associations in language processing. Along with lesion studies, single unit recordings, MRI, etc., PET has proven useful in functionally decomposing and localizing linguistic processes. Petersen et al. (1989) were among the first to use PET to study *lexical processing*—the processing of single words. Their structure-function assignments regarding semantic processing are at odds with those from Frith et al. 1991, a subsequent PET study of the same phenomena. Exploring the task differences between these studies will illustrate the challenge PET researchers face in choosing the right tasks. As PET researchers themselves fully realize, the potential of failing to do so is PET's Achilles' heel.

Petersen et al. 1989. The purpose of this study was to identify the brain areas related to the processing of single words in normal subjects. The session consisted of 7 scans involving 4 tasks:

> *Fixation task* (scan 1). Subjects were asked to attend to the crosshair on the monitor.
>
> *Passive sensory task(s).* Common English nouns were passively presented visually (scan 2) and aurally (scan 3). To isolate the modality-specific word-level coding, scan 1 was subtracted from each of the sensory scans.
>
> *Speech output task(s).* Subjects were to speak aloud each visually (scan 4) and aurally (scan 5) presented noun. Subtracting the sensory scans from the speech output scans isolated articulatory coding and motor output.
>
> *Semantic association or "generate use" task(s).* Subjects were asked to generate aloud a verb corresponding to each visually (scan 6) and aurally (scan 7) presented noun. Subtracting the speech output scans from these scans isolated semantic processing.

In the last set of subtractions, Petersen et al. reported overlapping activations in left anterior inferior prefrontal cortex, bilateral activation of the anterior cingulate, and activations in the right inferior lateral cerebellum. Because the cingulate is implicated in attention-demanding processing (see below) and the cerebellum is implicated in the coordination of motor behavior, Petersen et al. conclude that the frontal lobe is the locus of semantic processing. However, the traditional locus of semantic processing is Wernicke's area (in the temporal lobe). Accordingly, their assignment of that function to the frontal lobe was controversial, but not unjustified.

First, because there was not *any* significant temporal lobe activation during any level of lexical analysis upon visually presented words (Petersen and Fiez 1993, 522), the processing of visual linguistic stimuli seems to bypass Wernicke's area altogether, a result consilient with prior blood flow studies *not* using PET (Petersen et al. 1989, 165). Consequently, some other brain region(s) must be involved with storing the meaning of words and PET results led Petersen et al. to advance the alternative localization of this activity in the frontal lobe.

Second, that visual and auditory linguistic stimuli are processed independently by modality-specific pathways that have *independent* access to Broca's area is consistent with the notion that lexical processing occurs over a large number of areas, parallel routes, and a complex set of interconnections (Petersen et al. 1989, 153). While the assignment of a semantic role to the frontal lobe is at odds with some models, it is consilient with others, such as the *dual route model.*

A third and important source of consistency has emerged from subsequent PET studies of the same phenomena where the results were replicated.

Frith et al. 1991. Not every PET study of lexical processing replicated the Petersen et al. results. Frith et al. (1991), in a study of verbal fluency, assign the function of semantic processing to the temporal, not the frontal lobe. While this assignment is consistent with the traditional locus of semantic processing, it is worth noting that unlike the tasks chosen by Petersen et al., those chosen by Frith et al. each have an auditory component—a component requiring an increase in temporal lobe blood flow: in the *rest task*, subjects were asked to listen to a relaxation tape; in the *counting task*, subjects were asked to count from 1 until the scan was complete; for the *lexical decision task*, words and orthographicly regular nonwords were presented aurally at the rate of 2 every 5 seconds, and subjects had to respond with "correct" if the item was a word and "incorrect" if it was a nonword; for the *association task*, subjects were asked to generate words—namely, jobs—until the scan was complete; etc.

Since all these tasks required auditory processing, it is hardly surprising that Frith et al. report significant temporal lobe activations, something not reported by Petersen et al. for any level of processing upon visually presented words. Ignoring whether Frith et al. unpack the phonological, articulatory, and semantic aspects of the verbal fluency tasks, this much is clear: From the point of view of replicating Petersen et al. 1989, Frith et al.'s study was poorly designed. This illustrates just how problematic PET-based structure-function assignments may be. PET data are only as good as the ability of the tasks chosen for the study to invoke discrete underlying processes.

Attentional Processes. While cognitive psychology has differentiated tasks into those requiring attention and those that do not, it has offered little insight as to *how* the mechanisms of attention might work. PET, when combined with other tools employed in neuroanatomical mapping and in analyzing neural deficits, now offers the promise of advancing a functional decomposition and localization of attention processes. One contribution of this research has been to decompose attention into three different sets of processes, each of which has been associated with a different neural network. Even if this decomposition ultimately must be modified, this offers a first step into decomposing attention. We shall concentrate on two of these component systems.

Anterior Cingulate System. The anterior cingulate and its projections exhibits increased blood flow in a host of cognitive tasks requiring high-level executive control (e.g., tasks requiring divided attention, tasks requiring the resolution of conflict). This suggests to PET researchers that it might be the "central executive" controlling other cognitive processing (Posner et al. 1994). When assigning this function to the anterior cingulate, researchers do not appeal to PET data alone. For instance, there is a small group of patients with bilateral lesions to the cingulate that exhibit akinetic mutism—a disorder that allows patients to follow but not to initiate activities such as conversations. Such findings, along with lesion studies involving the cingulate, all support the bold hypothesis that the cingulate is, as Posner and Raichle (1994, 168) suggest, an "executive attention network."

What is quite remarkable about this proposal is that what seems to be localized in the cingulate is not a simple component process, but a very large task. The link with consciousness almost suggests that the cingulate is the seat of the soul. (Did Descartes just make a mistake in opting for the pineal gland rather than the cingulate?) Unlike the research on lexical processing, the work on the cingulate has yet to suggest a decomposition of the executive functions that are being attributed to it. Accordingly, this research has the flavor of a simple localization, and consequently, to provide little explanatory gain so far.

Posterior Parietal System. This attention system involves the superior colliculus, pulvinar, and the posterior parietal lobe. All three components show increased blood flow in tasks requiring subjects to select or maintain attention at a location. The important clue to the decomposition of function between these areas was provided by deficits exhibited by patients with lesions in these areas. Patients with lesions in the posterior parietal lobe are much worse than normals in disengaging attention from a location. Patients with lesions in the superior colliculus are much slower to redirect attention to a location. Patients with damage to the pulvinar had difficulty focusing in on a location. From this pattern of deficits, Posner proposed a circuitry involved in the posterior attention system:

> First, operations are carried out by the parietal lobe, which prepares for a contralateral shift of attention. Then the midbrain [superior colliculus] seems to have the major responsibility for car-

> rying out the shift. The thalamic area locks attention in place, allowing the subject to read out information at that spatial location. (1992, 12)

Aside from appeals to other sources of collateral evidence (e.g., electrical recording studies and studies of developmental timetables), Posner's analysis receives further support from the conceptual coherence and plausibility of the overall story. It seems like a sound engineering design. Different tasks are identified, each with relatively small computational demands, and there is a coherent account of how the systems performing the tasks interact. Thus, consistency with the results produced by other techniques and the overall theoretical coherence of the resulting theory together lend support to the PET results.

As plausible as this model is, we need to emphasize that no *direct* evidence is provided that a given area carries out precisely the task it is construed as performing. Not only is the evidence all *indirect*, it is subject to alternative interpretations. For instance, Cohen et al. (1994), relying on a connectionist model, offer such an alternative which denies the existence of a disengage mechanism in the posterior parietal cortex. Their model exhibits the same behavior as humans in showing slower response to falsely cued stimuli and, when lesioned, greater difficulty in disengaging from the falsely cued location. But the units that are lesioned are part of an interactive network that builds up attention, not disengages it from other sites. We do not pretend to settle this conflict, but only to note how alternative functional interpretations can be offered of a structure activated in PET studies.

Of the two attention systems described above, the posterior orienting system comes the closest to the goals of PET researchers of decomposing and localizing simple component cognitive tasks in specific brain regions. Yet, even here the connectionist simulation of Cohen et al. reveals the challenge of establishing the structure-function mapping. In other cases, such as the assignment of the executive control to the anterior cingulate, the results so far are *suggestive* of an important function of the cingulate, but do not yet support a decomposition into simple component cognitive processes.

5. The Limits and Promise of PET. While our focus has been on the epistemic challenges in the use of PET, our objective has not been to cast doubt upon PET and neuroimaging studies in general. To us they represent an extremely powerful and useful tool for developing a mechanistic account of cognitive processing. Rather, our concern has been to identify where epistemic issues arise in the development and use of such a new research tool and to explore how scientists attempt to answer these questions. What we have tried to show is that, while PET plays an important role in this emerging account of structure-function relations, it is not employed in isolation. Indeed, PET relies for its own epistemic credibility in large part on the consistency of its results with those of other techniques and the plausibility of the resulting analysis.

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