NeuroImage 84 (2014) 1101–1103

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Comments and Controversies

PET neuroimaging: Plenty of studies still need to be performed Comment on Cumming: "PET Neuroimaging: The White Elephant Packs His Trunk?"

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ARTICLE INFO

Article history:
Accepted 6 August 2013
Available online 15 August 2013

"The old order changeth, yielding place to new, …" (From *The Idylls of the King*, by Alfred Lord Tennyson).

But does it? In a recent commentary in this journal, Paul Cumming argues that positron emission tomography (PET) studies no longer seem to be making a significant contribution to understanding the neural substrate of normal human brain function (Cumming, 2014). He does this by providing a brief overview of the PET articles that appeared in NeuroImage during 2012. It is relevant to note that he is not asserting that brain PET is not playing an important role in clinical studies of patients with brain disorders. Indeed, his motivation for submitting his commentary was the decision by NeuroImage to set up a companion journal, NeuroImage Clinical, which resulted in a paucity of PET articles being sent to NeuroImage. His main conclusion is that PET is no longer a highly utilized tool for examining normal brain function. A major cause for this, according to Cumming, is the great expense and technical difficulty of doing PET compared to fMRI. He does not dispute, however, other concerns such as the use of radioactivity in PET, as well as limitations in spatial and temporal resolution.

We agree with much of what Dr. Cumming says, and think his article serves a very useful purpose in highlighting some of the changes occurring in the field of neuroimaging. Moreover, the commentary by Siebner et al. (2014) compliments the Cumming paper by addressing some of the ways that PET will continue to be an important member of the toolkit of methods employed to understand normal human brain functioning. We agree, but believe that Cumming didn't discuss thoroughly enough some crucial reasons to do the difficult and expensive task of using PET in certain normal subject studies. And as such, we feel that it is worth emphasizing that there are significant reasons to continue with brain PET, in spite of the expense and technical difficulties of performing a scan. In our commentary, we will focus on three types of studies that we think will continue to employ PET (and which will be appropriate for publication in NeuroImage). They are (1) certain activation studies that measure regional cerebral blood flow (rCBF) as an index of neural activity; (2) neurotransmitter studies; and, (3) multimodal studies.

PET rCBF activation studies will continue to play a pivotal role in cognitive neuroscience for a large class of studies that are particularly sensitive to certain problems endemic to BOLD fMRI. One such problem is the susceptibility artifact, which is especially prominent in anterior and ventral brain areas. Because of it, fMRI data from areas in the anteroventral temporal and frontal lobes often are unusable in conventional studies. A second problem is the noise generated by the gradient coils, which can adversely affect listening to auditory inputs and can make recording of spoken outputs difficult. The third problem is due to the movement artifacts that arise from speaking or other orofacial movements. While all three can impact studies investigating a variety of cognitive processes, studies of auditory and language processing can be particularly susceptible to these problems (Horwitz and Wise, 2008).

Brain areas where the susceptibility artifact is largest include the temporal pole and the ventral portion of the orbital frontal cortex. A number of studies have implicated the former in language processing. For example, Spitsyna et al. (2006) used rCBF PET to show common activation during implicit comprehension of spoken and written language in inferior and lateral regions of the left anterior temporal cortex and in lateral regions of the left temporal–parietal–occipital junction. Investigators using fMRI have tried to overcome this signal dropout by using high spatial resolution (Devlin et al., 2000), but such an approach often results in limited brain coverage, which in turn can interfere with a functional or effective connectivity analysis, since important network nodes may not be imaged (Kim and Horwitz, 2009).

The second problem – the loudness of the gradient coils – affects fMRI studies in a variety of ways, including making it difficult for a subject to hear auditory inputs, reducing the sensitivity of neural responses to heard auditory inputs, and interfering with the recording of spoken

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http://dx.doi.org/10.1016/j.neuroimage.2013.08.009

outputs. Among attempts to overcome these limitations, the most well-known is the use of sparse temporal sampling (e.g., Hall et al., 1999; Simonyan et al., 2009); however, this data acquisition protocol severely limits the types of experimental designs and analysis methods that can be employed. In comparison with fMRI, PET scanning is relatively quiet.

Artifacts arising from subject movement plague all fMRI studies, but they are particularly problematic for studies of voice and language production. Speaking in the scanner leads to a susceptibility artifact that is especially prominent in anterior and ventral frontal language areas. Moreover, speaking produces a movement artifact, which may or may not be removable using preprocessing algorithms. As with the problem of scanner noise discussed in the previous paragraph, an fMRI sparse-sampling design can be employed to circumvent this problem, but use of this technique imposes limitations on the experimental design. Recall that sparse temporal sampling is based on the fact that due to the hemodynamic delay, the BOLD response to neural activity is delayed for several seconds, whereas the susceptibility artifact to movement is immediate (Birn et al., 1999). Thus, scanning about 4–6 s following the voiced output allows the investigator to obtain uncontaminated data representing the neural response that led to the voiced output (e.g., Simonyan et al., 2009). However, the sparse sampling approach does not work for long duration auditory input (such as continuous speech) or output (such as producing a spoken narrative). PET can be used in such cases, as illustrated by a study comparing speech and American Sign Language production (Braun et al., 2001).

It is worth emphasizing that because language processing is unique to humans, ascertaining its neural correlates in healthy subjects can only be done by use of functional neural imaging, and thus for many real world aspects of language processing, rCBF PET will continue to be an important tool. Although some efforts in software development of preprocessing algorithms that can remove movement artifact are underway (e.g., Xu et al., 2011), rCBF PET still provides the most straightforward way to study continuous language function in normal humans.

The second type of study that employs PET and that will continue to be of importance to human cognitive neuroscience are those that image neurotransmitter function. Investigations of this sort were discussed by both Cumming (2014) and Siebner et al. (2014) in their articles. Both papers commented on current and future PET ligand development, and both were optimistic that the introduction of new ligands that target various neurotransmitter systems will increase the desire by research groups to employ PET. It is important to add that a combination of neuroreceptor mapping studies with rCBF PET would help identify the effects of rCBF on neurochemical processes. It is especially important for the newly developed ligands to establish that activity-related CBF does not have a confounding effect on the ligand's specific bindings values and the distribution of the tracer does not depend on rCBF, thus validating the use of a tracer (Fukumitsu et al., 2005; Ishiwata et al., 2008). Furthermore, combined rCBF and neuroreceptor measures may help derive information about the dynamic and plastic changes in both systems. For example, age-related changes in muscarinic cholinergic receptors have been described in a study that looked at the relationship between neuroreceptor distribution volume and rCBF changes in younger and older individuals (Kakiuchi et al., 2001).

The third type of study that will continue to employ brain PET consists of multimodal studies — those investigations in which different kinds of neuroimaging data are acquired in the same subject. This type of study was discussed by Siebner et al. (2014) in their commentary. They focused primarily on the use of scanners that can simultaneously perform PET and MRI, and we agree with them that this type of device will play a significant role in the future for the reasons they detail.

However, even if separate PET and MRI scans are acquired in different sessions, we feel that the scientific questions that can be addressed will be important enough to induce researchers to utilize a multimodal approach. Recently, a few studies have started using this approach to examine the interactions between brain function, structure and neurotransmission during complex cognitive processes, such as speaking and listening to music (Salimpoor et al., 2011; Simonyan et al., 2013). For example, we used PET imaging with ^{11}C-raclopride to measure the extent of endogenous dopamine release in the striatum and its influences on the organization of functional and structural striatal speech networks during the production of meaningful English sentences (Simonyan et al., 2013). Structural MR imaging estimated striatal–cortical white matter connectivity by means of diffusion tensor imaging, and striatal functional connectivity during speech production was obtained via fMRI. An important finding was the relative lateralization of dopamine release to the left hemisphere during sentence production, in spite of symmetric structural connectivity.

One other aspect of multimodal imaging needs to be mentioned, and that is the general issue of combining neural data from many sources into a coherent account of how the neural architecture of the brain mediates specific cognitive functions. One of us (BH) has argued over the years that the way to do this is to integrate these multiple and diverse types of neural data into large-scale, biologically realistic neural models that can simulate multiple types of data that can, in turn, be compared with experiment (Horwitz, 2005; Horwitz et al., 1999). In recent years, a number of groups have begun to utilize such an approach (e.g., Arbib et al., 2000; Deco et al., 2004; Ritter et al., 2013; Tagamets and Horwitz, 1998). As brain PET begins to supply more information on neurotransmitter release during different cognitive tasks, these data will be employed in the neural modeling efforts.

In conclusion, we agree with Cumming (2014) that the expense and difficulty of brain PET are such that fMRI (and EEG/MEG) will continue to be the dominant functional neuroimaging tool in the near future. However, brain PET should not be written off; not only will it continue to be employed in studies of patient populations, it also will be continuously utilized to study normal brain cognitive processing for a variety of functions that are difficult to perform with fMRI. Importantly, brain PET also will provide valuable insight into human neurochemistry, especially in terms of neurotransmitter function. Finally, data derived using brain PET will be necessary for incorporation into neural modeling that will form the basis for providing detailed hypotheses about the neural basis of human cognition.

Acknowledgments

This work was supported by the Intramural Research Program of the National Institute on Deafness & Other Communication Disorders, NIH (BH) and NIH grant R00DC009629 (KS).

Conflict of interest

The authors declare no conflicts of interest.

References

Arbib, M.A., Billard, A., Iacoboni, M., Oztop, E., 2000. Synthetic brain imaging: grasping, mirror neurons and imitation. Neural Netw. 13, 975–997.
Birn, R.M., Bandettini, P.A., Cox, R.W., Shaker, R., 1999. Event-related fMRI of tasks involving brief motion. Hum. Brain Mapp. 7, 106–114.
Braun, A.R., Guillemin, A., Hosey, L., Varga, M., 2001. The neural organization of discourse: an H215O-PET study of narrative production in English and American sign language. Brain 124, 2028–2044.
Cumming, P., 2014. PET neuroimaging: the white elephant packs his trunk? NeuroImage 84, 1094–1100.
Deco, G., Rolls, E.T., Horwitz, B., 2004. 'What' and 'where' in visual working memory: a computational neurodynamical perspective for integrating fMRI and single-cell data. J. Cogn. Neurosci. 16, 683–701.
Devlin, J.T., Russell, R.P., Davis, M.H., Price, C.J., Wilson, J., Moss, H.E., Matthews, P.M., Tyler, L.K., 2000. Susceptibility-induced loss of signal: comparing PET and fMRI on a semantic task. NeuroImage 11, 589–600.

Fukumitsu, N., Ishii, K., Kimura, Y., Oda, K., Sasaki, T., Mori, Y., Ishiwata, K., 2005. Adenosine A1 receptor mapping of the human brain by PET with 8-dicyclopropylmethyl-1-11C-methyl-3-propylxanthine. J. Nucl. Med. 46, 32–37.

Hall, D.A., Haggard, M.P., Akeroyd, M.A., Palmer, A.R., Summerfield, A.Q., Elliott, M.R., Gurney, E.M., Bowtell, R.W., 1999. "Sparse" temporal sampling in auditory fMRI. Hum. Brain Mapp. 7, 213–223.

Horwitz, B., 2005. Integrating neuroscientific data across spatiotemporal scales. C. R. Biol. 328, 109–118.

Horwitz, B., Wise, R.J.S., 2008. PET research of language. In: Stemmer, B., Whitaker, H.A. (Eds.), Handbook of the Neuroscience of Language. Academic Press, Amsterdam, pp. 71–80.

Horwitz, B., Tagamets, M.-A., McIntosh, A.R., 1999. Neural modeling, functional brain imaging, and cognition. Trends Cogn. Sci. 3, 91–98.

Ishiwata, K., Ishii, K., Kimura, Y., Kawamura, K., Oda, K., Sasaki, T., Sakata, M., Senda, M., 2008. Successive positron emission tomography measurement of cerebral blood flow and neuroreceptors in the human brain: an 11C-SA4503 study. Ann. Nucl. Med. 22, 411–416.

Kakiuchi, T., Ohba, H., Nishiyama, S., Sato, K., Harada, N., Nakanishi, S., Tsukada, H., 2001. Age-related changes in muscarinic cholinergic receptors in the living brain: a PET study using N-[11C]methyl-4-piperidyl benzilate combined with cerebral blood flow measurement in conscious monkeys. Brain Res. 916, 22–31.

Kim, J., Horwitz, B., 2009. How well does structural equation modeling reveal abnormal brain anatomical connections? An fMRI simulation study. NeuroImage 45, 1190–1198.

Ritter, P., Schirner, M., McIntosh, A.R., Jirsa, V.K., 2013. The virtual brain integrates computational modeling and multimodal neuroimaging. Brain Connect. 3, 121–145.

Salimpoor, V.N., Benovoy, M., Larcher, K., Dagher, A., Zatorre, R.J., 2011. Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. Nat. Neurosci. 14, 257–262.

Siebner, H.R., Strafella, A.P., Rowe, J.B., 2014. The white elephant revived: A new marriage between PET and MRI. NeuroImage 84, 1104–1106.

Simonyan, K., Ostuni, J., Ludlow, C.L., Horwitz, B., 2009. Functional but not structural networks of the human laryngeal motor cortex show left hemispheric lateralization during syllable but not breathing production. J. Neurosci. 29, 14912–14923.

Simonyan, K., Herscovitch, P., Horwitz, B., 2013. Speech-induced striatal dopamine release is left lateralized and coupled to functional striatal circuits in healthy humans: a combined PET, fMRI and DTI study. NeuroImage 70, 21–32.

Spitsyna, G., Warren, J.E., Scott, S.K., Turkheimer, F.E., Wise, R.J., 2006. Converging language streams in the human temporal lobe. J. Neurosci. 26, 7328–7336.

Tagamets, M.-A., Horwitz, B., 1998. Integrating electrophysiological and anatomical experimental data to create a large-scale model that simulates a delayed match-to-sample human brain imaging study. Cereb. Cortex 8, 310–320.

Xu, Y., Abdulsabur, N., Liu, S., Chow, H.M., Braun, A.R., 2011. Denoising the speaking brain: characterizing and removing imaging artifacts in BOLD fMRI of continuous overt speech production. 3rd Annual Neurobiology of Language Conference.