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Integrated and automated data analysis method for neuronal activation studies using O-15 water PET

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INTRODUCTION:

Neuronal activation studies using positron emission tomography (PET) have been reported to be a useful tool to examine functional localization and organization relating to specific tasks in human brains. Fox and co-workers (1) initially proposed a novel method of data analysis for PET activation studies, in which cerebral blood flow (CBF) images from multiple subjects are spatially standardized and averaged to reveal consistent local CBF changes. When analyzing activation data in this manner, several factors inherent in individual neurophysiologic and neuroanatomic variations, as well as PET measurements, should be taken into account. To achieve objective, reliable, and reproducible data analysis, we have implemented and validated an integrated and automated method for O-15 water PET activation studies, and have tested the method using common activation paradigms.

METHODS AND VALIDATION:

The method assumes repeated CBF measurements under specific 'stimulation' and 'baseline' conditions in multiple subjects. After removing the subject's head movement among serial scans by a three-dimensional image co-registration technique, stimulation and baseline image sets are averaged separately in a subject, creating a pair of average stimulation and baseline image sets. The co-registration algorithm uses a new image matching criterion which maximizes the number of voxels with less than a preset percent difference. Each image set is transformed to stereotactic coordinates according to the intercommissural (AC-PC) line automatically detected in the PET image set (2,3). After linear correction of the brain size followed by three-dimensional non-linear regional anatomical standardization, the stimulation and baseline image sets are normalized to global counts, and then averaged separately in the stereotactic coordinates, forming mean and variance for each condition on pixel-by-pixel basis. Image sets were smoothed with a three-dimensional Gaussian filter prior to the inter-subject averaging. The regional anatomical standardization technique uses a combination of edge detection, landmark detection assuming major neuronal pathways, and three-dimensional warping (4). The means are compared by t statistics, calculating a t value between two conditions for each pixel in the brain. After transforming t values to Z scores, a statistical threshold is derived from a modification of the stochastic formulation proposed by Friston and co-workers (5) in three dimensions. Peaks in the Z score image are searched throughout the whole brain and reported with normalized CBF changes and stereotactic coordinates. Areas of significant change are also superimposed onto a standard magnetic resonance image for visual interpretation.

We validated each step in the integrated method separately. Accuracy of the co-registration was assessed both visually, creating a smoothed subtraction image between co-registered images, and through the use of phantom studies. Stimulation and baseline image sets from eighteen subjects (short-term memory) as well as paired dissimilar CBF image sets from eighteen subjects (carotid artery occlusion study) were examined. Accuracy of the stereotactic re-orientation has been reported previously (3). Effects from the regional anatomical standardization were evaluated in two ways. First, we visually inspected standard deviation (SD) images created on pixel-by-pixel basis from CBF images of eighteen subjects with and without the standardization. Higher SD values were expected where mismatches of the regional gray matter exist. Second, vibratory and visual activation studies were conducted in five subjects, and CBF changes were measured in the primary sensory cortex and visual cortex with and without the standardization. For the statistical threshold, estimated and observed false positive rates were compared using 20 three-dimensional simulated Gaussian process (256 x 256 pixel matrix, 120 slices, 1.125 mm voxel in size). Comparison was done by changing image smoothness

(determined by a convolved Gaussian filter) and threshold. Finally, we applied the method to activation studies of vibratory, visual, and thermal pain stimulations. In the vibratory (vibrator, left hand, n=5) and thermal pain (thermal probe 50°C, left forearm, n=9) stimulations, three stimulation and three baseline scans were obtained for each subject following intravenous bolus administration of 66 mCi O-15 water. In the visual stimulation (reversing checkerboard, n=5), four stimulation and four baseline scans were obtained for each subject following administration of 50 mCi O-15 water. Each scan was acquired over 60 seconds, starting 5 seconds after initial radioactivity reached the brain. Absolute counts of the images were used for the analysis.

RESULTS AND COMMENTS:

The co-registration technique clearly corrected head movement among serial scans in each subject. Without the co-registration, rim-like artifacts in subtraction images were observed in eighteen stimulation-baseline paired scans. These artifacts disappeared in all cases after the co-registration procedure. Averaged absolute values of head movements corrected by the algorithm in x (right-left), y (antero-posterior), z (ventro-dorsal) translations, and xy, yz, xz rotations were 0.4 ± 0.4, 0.5 ± 0.4, 0.8 ± 0.6 pixels, and 1.0 ± 0.8, 1.7 ± 1.8, 0.8 ± 0.6 degrees, respectively. The algorithm can correct for head movements as small as a few tenths of a pixel or degree. Furthermore, the algorithm worked well on the eighteen dissimilar paired image sets, which confirmed that accuracy of the algorithm was fairly insensitive to CBF alterations in a same subject.

The SD image created without regional anatomical standardization showed high SD values around the superior frontal and parietal cortices, the occipital cortex, the inferior temporal cortex, the cerebellum, and the inner surface of the caudate. Those high SD values disappeared (fronto-parietal, cerebellum) or were reduced (occipital, inferior temporal, caudate) by the regional standardization procedure. The magnitude of the CBF change due to the stimulations measured in averaged subtraction images was increased by 33% in the primary sensory cortex and 11% in the primary visual cortex following the regional standardization. The smaller improvement in the primary visual cortex may limit this standardization technique in such areas.

Estimated false positive rates from the modified three-dimensional stochastic formulation roughly agreed with observed false positive rates in the simulation studies. When the threshold was increased, the estimation tended to be more conservative. At typical smoothness (15 - 20 mm, full-width-at-half-maximum) and threshold ($Z = 3.5 - 4.0$) in actual data, the estimated rates remained conservative. A possible alternative approach would be use of the Euler characteristic recently reported by Worsley and co-workers (6).

In the vibratory activation study, significant CBF increases were observed in the contralateral postcentral gyrus, cerebellum, and supplementary motor area ($p = 0.00005$, adjusted $p = 0.05$). In the visual activation study, multiple foci of significant CBF increase were observed in the primary visual cortex ($p = 0.00006$). In the pain activation study, significant CBF increases were observed in the anterior cingulate, midbrain, cerebellar vermis, contralateral thalamus, and contralateral secondary sensory cortex ($p = 0.0001$). A small but significant focus in the midbrain indicates possible involvement of periaqueductal gray matter in the spinomesencephalic pathway in pain perception.

The integrated and automated method enables objective and reproducible data analysis for O-15 water PET activation studies. The method also can be combined with other statistical tests (i.e., correlation) and is applicable to various study designs. These advantages should facilitate applications of PET neuronal activation studies.

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