CHAPTER 26

Functional Brain Mapping and Activation Likelihood Estimation Meta-Analysis

Angela R Laird, Jack L Lancaster and Peter T Fox

In recent years, the increasing richness of data generated by fMRI and PET brain mapping studies has encouraged the growth of meta-analysis research. In response to this progress, a new method of quantitative, voxel-based meta-analysis, termed activation likelihood estimation (ALE), has been developed and applied in a number of cognitive and perceptual domains. Here, the method is discussed and findings from a meta-analysis of the Stroop task are highlighted.

26.1 META-ANALYSIS OF THE FUNCTIONAL BRAIN MAPPING LITERATURE

Research in human functional brain mapping (HFBM) using functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) has increased at an astonishingly fast rate over the past ten years, and this activity has generated a deluge of published articles in the field. As a consequence, there exists an extremely rich resource available and suitable for large-scale data mining and meta-analysis of data designed to localize activation patterns of various behavioral paradigms. This list of paradigms includes, but is not limited to, tasks such as delayed match to sample, Stroop, mental rotation, saccades, semantic discrimination, and finger tapping. While any single functional neuroimaging study can

highlight the neural activity that occurs in response to a unique combination of task implementation, imaging parameters, and scanning environment, combining the data obtained from multiple, independent studies gives a measure of the robustness of the observed activation patterns.

There are a number of imaging standards in HFBM, but there are two in particular that allow for quantitative meta-analysis of fMRI and PET data. First, nearly all published studies include the analysis step of spatial normalization in which individual subject brains are warped and transformed into a standard brain space, referenced to a brain atlas. Second, it has become very common for researchers to report locations of brain activation in response to a stimulus or task as stereotactic (x, y, z) coordinates, reflecting the centers of mass of the activated brain regions. These two standards, one an analysis standard and the other a reporting standard, have encouraged the growth of a new category of meta-analysis possible with functional neuroimaging data.

Meta-analysis, generally defined as the *post hoc* combination of independently performed studies to better estimate a parameter of interest, has been utilized for decades in many medical fields.[1–3] Traditional meta-analyses often merge nonsignificant results to test for significance in pooled data. In human functional brain mapping, function-location meta-analysis has emerged as an analysis tool in which statistically significant effects from published studies are combined to create predictive models of neural systems.[4,5]

Function-location meta-analysis must be distinguished from traditional literature review. The most common method of literature review in HFBM is to construct a table or figure that summarizes the activation patterns of a given group of studies. This can be done either by plotting stereotactic coordinates of activation on a standard brain, organizing the coordinates into a bar graph that is segregated by cortical and subcortical regions, or by creating a table that individually lists these foci in text format. These methods are widely used for finding agreement among studies with similar experimental contrasts and are well accepted.[6–12] However, as

opposed to meta-analysis, these reviews do not involve any quantitative analysis of the patterns of brain activations, yield no formal estimate of probability, and are difficult to visually interpret.

26.2 ACTIVATION LIKELIHOOD ESTIMATION (ALE)

In 2002, Peter Turkeltaub[13] presented a new and quantitative meta-analysis method, termed activation likelihood estimation, or ALE.[13] In this first ALE publication, the method was presented, applied in a meta-analysis of single word reading PET studies, and verified in an fMRI reading task. Around the same time, Chein *et al.*[14] published a meta-analysis of working memory studies using an analysis method termed aggregated Gaussian-estimated sources (AGES), which follows the same general procedure detailed by Turkeltaub *et al.*[13] The simultaneous development by two groups of the same voxel-based meta-analytic tool is strongly indicative of the timeliness and utility of this form of meta-analysis. For simplicity, we henceforth refer to this method as an ALE meta-analysis.

In ALE, each x, y, z coordinate of activation is thought of not as a single point of activation, but rather as the center of a Gaussian probability distribution. While this is a rough approximation to the real-life complexity of three-dimensional clusters of activation in brain space, Turkeltaub's results were surprisingly robust and introduced a new era of meta-analysis research in functional neuroimaging. In an ALE meta-analysis, three-dimensional coordinates in stereotactic space are collected and filtered from a number of similar studies. These coordinates are typically published relative to Talairach space[15] or Montreal Neurological Institute (MNI) space[16] and must be spatially renormalized to a single template. This transformation has generally been performed using the mni2tal transform.[17] However, a recent study has shown that the mni2tal transform is not optimal and has recommended best-fit coordinate transforms for use with different brain templates (ICBM-152 and MNI-305) and different software packages (FSL and SPM2).[18] Once all the included foci in the meta-analysis refer to locations in a single stereotactic space, the ALE analysis begins.

26.2.1 The ALE Statistic

Each reported coordinate (focus) is modeled by a three-dimensional Gaussian distribution, defined by a user-specified FWHM (full width at half maximum). If X_i denotes the event that the i^{th} focus is located in a given voxel, then the probability of X_i occurring at voxel x, y, z is

$$\Pr(X_i) = \frac{\exp(-d_i^2/2\sigma^2)}{(2\pi)^{3/2}\sigma^3} \cdot \Delta V \qquad (1)$$

where d_i is the Euclidean distance from the center of the voxel to the i^{th} focus, σ is the standard deviation of the Gaussian distribution, and $\Pr(X_i)$ satisfies $0 \leq \Pr(X_i) \leq 1$. The Gaussian probability density is multiplied by $\Delta V = 8\,\text{mm}^3$ (corresponding to voxel dimension of 2mm × 2mm × 2 mm) in order to obtain the probability estimate for the entire voxel volume, instead of its central point. If X denotes the event that *any* foci are located within a given voxel, then $\Pr(X)$ is defined as the union of all $\Pr(X_i)$, where $\Pr(X_i)$ is shown in Eq. (1). This value, $\Pr(X)$, is defined as the ALE statistic and quantifies the likelihood of activation at a given voxel and task, as determined by the chosen set of studies from the literature.

26.2.2 Permutation Tests

The ALE statistic is computed at every voxel in the brain. In order to make a valid assessment of the significance of the results, a nonparametric procedure for testing the statistic images was developed using a permutation test.[19] To test the null hypothesis that the foci are uniformly spread throughout the brain, x random foci are generated, where x equals the number of foci included in the ALE meta-analysis. The corresponding ALE values for these random foci are computed. This process of randomization and computation of relabeled statistics is repeated 1 000–10 000 times, depending on the desired precision of the test. The set of ALE values calculated from the random foci forms the null distribution of the test statistic. A whole-brain histogram is computed in which the null hypothesis of uniformly distributed foci is rejected for voxels with an ALE value greater than the critical threshold. The critical threshold is defined as the $100(1-\alpha)^{\text{th}}$ percentile of the permutation distribution, where α refers to the desired level of significance.

26.2.3 Modifications to the ALE Approach

When ALE was introduced in 2002, a discussion of its limitations and areas in need of further development were provided.[13] In response to this discussion, two areas of interest were subsequently developed and tested.[20] First, the permutation test proposed by Turkeltaub *et al.* was improved in order to more accurately derive null distributions for the ALE statistic using a correction for the multiple comparisons problem that controls for the false discovery rate.[21,22] Second, a reliable method testing for the differences between two ALE meta-analyses was established. These modifications to the ALE method are currently distributed with an image-based graphical user interface as part of the BrainMap database project (http://brainmap.org). BrainMap is a free, community database of published functional neuroimaging results in the form of Talairach or MNI coordinates,[23,24] and is committed to continued support and development of advanced meta-analysis techniques, including ALE.

26.3 ALE META-ANALYSES OF HUMAN COGNITION AND PERCEPTION

In May 2005, as a result of a virtual workshop on meta-analysis techniques,[25] the journal, *Human Brain Mapping*, published the "Special Issue on Meta-Analysis in Functional Brain Imaging." This issue included three methodology articles on ALE and the analysis of meta-analysis networks[20,26,27] and twelve ALE meta-analyses of human cognition and perception. Specifically, nine ALE meta-analyses were presented on various cognitive tasks such as

the Stroop task,[28] switching tasks,[29] the Wisconsin Card-Sorting task,[30] the n-back working memory task in healthy subjects[31] and schizophrenic subjects,[32] object naming,[33] phonological processing of Chinese characters,[34] reading in Western and Eastern languages,[35] and fluent *vs* stuttered speech production.[36] In addition, three meta-analyses were published in the special issue on perceptual processes, including audition,[37] pain perception,[38] and vision.[39] Presented below are the highlights of the meta-analysis of the Stroop task.

26.3.1 Meta-Analysis of Stroop Interference Studies

In the Stroop task, subjects view color names presented in varying ink colors and are asked to name the color of the ink, while ignoring the word.[40] In the congruent condition, the color names match their displayed ink color. In the incongruent condition, the words are presented in non-matching ink colors (e.g. "blue" presented in red ink). The Stroop task is widely used to study inhibition and attentional control since correct performance in color naming often competes with the relatively automatic tendency to perform word reading.

An ALE meta-analysis of all published neuroimaging studies investigating the Stroop effect was performed to identify the regions of concordance across the published set of Stroop papers in order to more fully understand the detection of conflict and response selection in the human brain.[28] To reach this objective, a comprehensive literature search was carried out using Medline to determine the fMRI and PET Stroop studies that published Talairach or MNI coordinates of activation locations. From this set of studies, the included contrasts (Incongruent — Control) were filtered to eliminate non-standard task variations (counting Stroop, emotional Stroop), and only include group activation data from normal subjects. This filtering isolated 19 Stroop studies (13 fMRI and 6 PET) with 19 contrasts, containing a total of 205 foci. A plot of these foci is presented on a standard glass brain in Fig. 1(A).

This group of Stroop coordinates was then segregated by response modality. The studies were parsed into two different groups based on use of a button press response (manual Stroop;

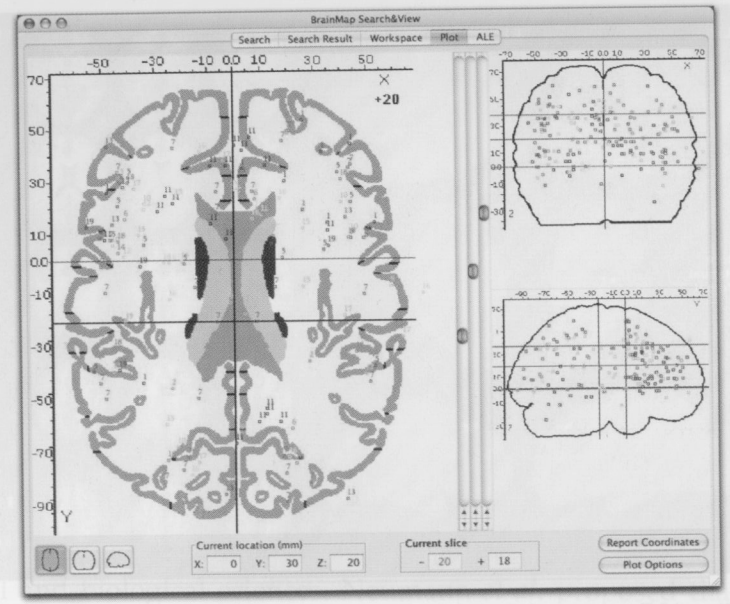

Fig. 1(A). Selected contrasts from the Stroop literature yielded a total of 205 foci, which are viewed in Talairach space in the BrainMap database java-based application *Search & View*. In this image, each color identifies a paper within the BrainMap environment and the number displayed along with each focus refers to the experiment within the corresponding paper; the circles can be changed to different symbols for identification purposes. Pooling the results of 19 experiments onto a single brain resulted in a diffuse pattern of activation across all lobes, with some clustering visually evident in the frontal lobes.

six studies) or a covert or overt speech response (verbal Stroop; thirteen studies). Three different ALE maps were computed for all Stroop studies, Stroop studies that required an overt or covert verbal response, and Stroop studies that required a manual response [Fig. 1(B)].

The ALE meta-analysis of all Stroop studies revealed high ALE values in the limbic, frontal, and parietal lobes. The verbal Stroop map revealed regions of high ALE values in the left inferior frontal gyrus (IFG) near BA 44 and bilateral insula, two regions commonly involved in articulation. In contrast, the manual Stroop map revealed a parietal involvement more extensive than seen in the verbal Stroop and an absence of concordance in the speech production

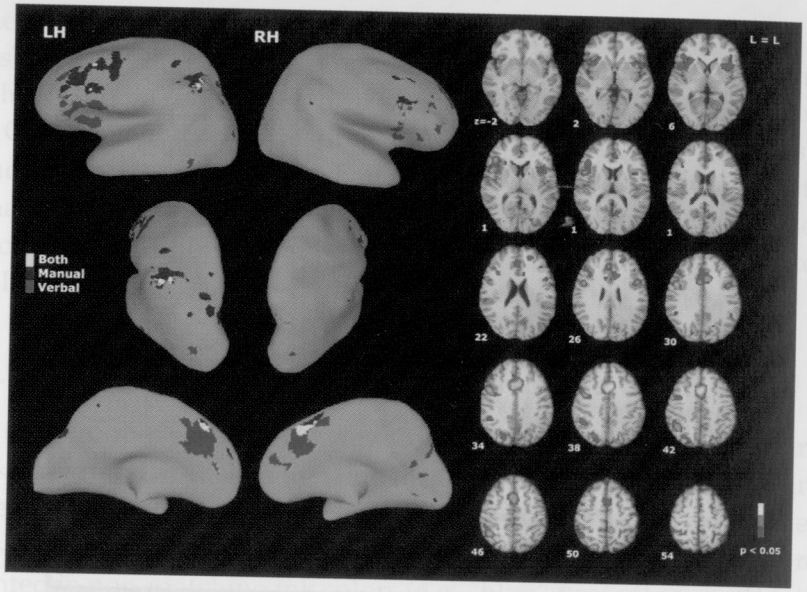

Fig. 1(B). ALE meta-analyses of the Stroop task were performed on renormalized Talairach coordinates from all studies, from studies that utilized a verbal speech response, and from studies that utilized a manual button press response. ALE values were computed at each voxel in the brain using a FWHM of 12 mm. Statistical significance was determined using a permutation test of randomly generated foci for 5000 permutations, corrected for multiple comparisons using the false discovery rate.[20,22] Thresholded ALE maps are viewed at a significance level of $p < 0.05$. On the right, the ALE map of the pooled Stroop foci is viewed in axial slices. On the left, the ALE map of verbal (red) and manual (blue) Stroop foci is viewed as a composite image (overlap = yellow) on a 3D brain surface.

areas observed in the verbal Stroop (BA 44 and insula). Clearly, while the Stroop task is essentially a verbal task and it is reasonable to assume that some form of covert vocalization occurs during the manual Stroop, it can be seen in Fig. 1(B) that the two response modalities display different activation patterns due to a stronger emphasis on vocalization and articulation in the verbal as opposed to manual Stroop task. When the manual and verbal Stroop ALE results are viewed in a composite image, regions of overlap were observed in the anterior cingulate, left inferior parietal lobule, and bilateral inferior frontal junction. The inferior frontal junction is located between the precentral gyrus and the inferior frontal gyrus, and is known

to be involved during tasks of cognitive control.[29,41] Based on these results, these regions have been isolated as major components of the network for response conflict resolution in the Stroop task.

26.4 ANALYSIS OF META-ANALYSIS NETWORKS (RDNA AND FSNA)

As described above, ALE can be used to identify the network involved in a given paradigm or behavioral domain; however, the ALE methodology does not include a technique to evaluate the relationships between nodes in the identified network. In response to this, Neumann *et al.*[26] published a method of investigating interregional connectivity based on replicator dynamics, a strategy based on the dynamics of competitive growth that is well established in social and biological sciences. Neumann *et al.* proposed that this replicator dynamics network analysis (RDNA) be used to isolate cortical networks that are activated most often together across multiple studies. The replicator dynamics approach can be used to identify subordinate networks within a larger network (e.g. to separate a perceptual subsystem from a motor subsystem in a cued-response paradigm). This function is based on analysis of a co-occurrence matrix, in which each element indicates how often a given pair of activation maxima is found to be coactivated in a given study.[26,42] Co-occurrence networks determined by ALE meta-analysis are assumed to be the summation of subnets. The fractional contribution of each subnet affects co-occurrence of the whole network.

In an RDNA analysis, the ALE method is first used to identify the regional nodes of activation from individual coordinates in multiple studies. Next, the occurrence of each of these nodes in the included studies is recorded. Third, the co-occurrence matrix is computed for the activation nodes. Last, the replicator process is applied to identify the dominant network.

Neumann *et al.*[26] presented an RDNA analysis of the Stroop task to illustrate their new method. In this example, the ALE meta-analysis identified 15 activation nodes. The replicator process

isolated five of these nodes to be the dominant network, including the presupplementary motor area, left inferior frontal sulcus extending onto the middle frontal gyrus, bilateral anterior cingulate, and the left inferior frontal junction. The replicator process assigned the highest connectivity weight to the right anterior cingulate node, which was the second largest node and showed the second highest number of co-occurrences. The highest number of co-occurrences was found for the inferior frontal sulcus, which was assigned the second highest connectivity weight, but was the smallest node in the network. These results demonstrate that connectivity weight is determined by the relationship between different activation nodes and is a function of co-occurrence, the extent of the ALE clusters, and the magnitude of the ALE scores.

The network analysis technique based on replicator dynamics (RDNA) presented by Neumann *et al.*[26] introduced the first application of meta-analysis data to network analysis Lancaster *et al.*[27] examined both RDNA and a similar method known as fractional similarity network analysis (FSNA). Whereas the RDNA method used by Neumann *et al.* was applied to determine the dominant subset of nodes, the FSNA method determines the complete subsets of the data using binary pattern matching. Lancaster *et al.* chose to study both RDNA and FSNA on the pooled Stroop data set (19 studies with 205 foci) from the meta-analysis performed by Laird *et al.*[28] This dataset was similar to that used by Neumann *et al.*, but included six additional studies. This pooled Stroop dataset was first analyzed using ALE, and yielded 13 nodes ($p < 0.01$). RDNA on this data set reported a dominant network of only two nodes (anterior cingulate and left inferior frontal junction), which contrasted from the five-node network identified as dominant in Ref. 26. However, modifying RDNA to return multiple maximal cliques, resulted in finding a five-node maximal clique consistent with the five-node network reported by Neumann *et al.*[26] Applying FSNA to the same Stroop data set revealed several important segregations of the data. The two cingulate clusters were parsed into different subnets. This is consistent with the previous determination of somatotopy within the cingulate motor area;[28] however, in the case of FSNA this parcellation into different subnets was done using the pooled Stroop data, and not by performing separate ALE analyses based on response modality. Both RDNA[26] and FSNA[27] have proved to be interesting extensions of the ALE meta-analysis method, and it is hoped that further investigation of these techniques will yield critical information concerning meta-analysis networks of cognition and perception.

26.5 CONCLUDING REMARKS

The utility of the ALE meta-analysis method is well established, and ALE has proved capable in illustrating differences in task stimulus or response modalities,[28,31,38] baseline conditions,[33] and normal *vs* diseased subject groups.[32,36,43] However, the true potential of connectivity analysis of meta-analysis networks remains yet to be discovered. While establishing these function-location relationships and uncovering areas of functional dissociation within the cortex has been a primary focus of research, more investigators are progressing from simple identification of network nodes towards studying the interactions between brain regions Neumann *et al.*[26] and Lancaster *et al.*[27] provided a path forward in this direction using their respective methods of replicator dynamics network analysis (RDNA) and fractional similarity network analysis (FSNA). Future work in this area will certainly involve probing network connection from meta-analysis data, perhaps using this information to inform networks for structural equation modeling[44,45] or dynamic causal modeling.[46,47]

References

1. Conn HO, Interpretation of data from multiple trials: A critical review, *J Intern Med* **241**: 177–183, 1997.
2. Mosteller F, Colditz GA, Understanding research synthesis (meta-analysis), *Annu Rev Public Health* **17**: 1–23, 1996.
3. Petitti DB, Meta-analysis and endocrinology, *Endocrinol Metab Clin North Am* **26**: 31–44, 1997.
4. Fox PT, Lancaster JL, Mapping context and content: The BrainMap model, *Nature Rev Neurosci* **3**: 319–321, 2002.

5. Fox PT, Parson LM, Lancaster JL, Beyond the single study: Function/location meta-analysis in cognitive neuroimaging, *Curr Opin Neurbiol* **8**: 178–187, 1998.
6. Barch DM, Braver TS, Akbudak E, Conturo T, *et al.*, Anterior cingulate cortex and response conflict: Effects of response modality and processing domain, *Cereb Cortex* **11**: 837–848, 2001.
7. Becker JT, MacAndrew DK, Fiez JA, A comment of the functional localization of the phonological storage subsystem of working memory, *Brain Cogn* **41**: 27–38, 1999.
8. Buckner RL, Petersen SE, What does neuroimaging tell us about the role of prefrontal cortex in memory retrieval? *Sem Neurosci* **8**: 47–55, 1996.
9. Bush G, Luu P, Posner MI, Cognitive and emotional influences in anterior cingulate cortex, *Trends Cogn Sci* **4**: 215–222, 2000.
10. Fiez JA, Raife EA, Balota DA, Schwarz JP, *et al.*, A positron emission tomography study of the short-term maintenance of verbal information, *J Neurosci* **16**: 808–822, 1996.
11. Owen AM, The functional organization of working memory processes within human lateral frontal cortex: The contribution of functional neuroimaging, *Eur J Neurosci* **9**: 1329–1339, 1997.
12. Picard N, Strick PL, Motor areas of the medial wall: A review of their location and functional activation, *Cereb Cortex* **6**: 342–353, 1996.
13. Turkeltaub PE, Eden GF, Jones KM, Zeffiro TA, Meta-analysis of the functional neuroanatomy of single-word reading: Method and validation, *Neuroimage* **16**: 765–780, 2002.
14. Chein JM, Fissell K, Jacobs S, Fiez JA, Functional heterogeneity within Broca's area during verbal working memory, *Physiol Behav* **77**: 635–639, 2002.
15. Talairach J, Tournoux P, Coplanar stereotaxic atlas of the human brain, Thieme, New York, 1988.
16. Collins DL, Neelin P, Peters TM, Evans AC, Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space, *J Comput Assist Tomogr* **18**: 192–205, 1994.
17. Brett M, (1999), The MNI brain and the Talairach atlas, Cambridge Imagers. http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html.
18. Lancaster JL, Tordesillas-Gutierrez D, Martinez M, Salinas F, *et al.*, Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template, *Hum Brain Mapp*, 2007.
19. Good P, Permutation tests: A practical guide to resampling methods for testing hypotheses, Springer-Verlag, New York, 1994.

20. Laird AR, Fox PM, Price CJ, Glahn DC, *et al.*, ALE meta-analysis: Controlling the false discovery rate and performing statistical contrasts, *Hum Brain Mapp* **25**: 155–164, 2005.
21. Benjamini Y, Hochberg Y, Controlling the false discovery rate: A practical and powerful approach to multiple testing, *J R Stat Soc Ser B* **57**: 289–300, 1995.
22. Genovese CR, Lazar NA, Nichols TE, Thresholding of statistical maps in functional neuroimaging using the false discovery rate, *Neuroimage* **15**: 870–878, 2002.
23. Laird AR, Lancaster JL, Fox PT, BrainMap: The social evolution of a human brain mapping database, *Neuroinformatics* **3**: 65–78, 2005.
24. Fox PT, Laird AR, Fox SP, Fox PM, *et al.*, Lancaster JL, Experimental design taxonomy of the BrainMap database: Description and validation, *Hum Brain Mapp* **25**: 185–198, 2005.
25. Fox PT, Laird AR, Lancaster JL, Coordinate-based voxel-wise meta-analysis: Dividends of spatial normalization. A report of a virtual workshop, *Hum Brain Mapp* **25**: 1–5, 2005.
26. Neumann J, Lohmann G, Derrfuss J, von Cramon DY, Meta-analysis of functional imaging data using replicator dynamics, *Hum Brain Mapp* **25**: 165–173, 2005.
27. Lancaster JL, Laird AR, Fox PM, Glahn DC, *et al.*, Automated analysis of meta-analysis networks, *Hum Brain Mapp* **25**: 174–184, 2005.
28. Laird AR, McMillan KM, Lancaster JL, Kochunov P, *et al.*, A comparison of label-based review and activation likelihood estimation in the Stroop task, *Hum Brain Mapp* **25**: 6–21, 2005.
29. Derrfuss J, Brass M, Neumann J, von Cramon DY, Involvement of the inferior frontal junction in cognitive control: Meta-analyses of switching and Stroop studies, *Hum Brain Mapp* **25**: 22–34, 2005.
30. Buchsbaum BR, Greer S, Chang W-L, Berman KF, Meta-analysis of neuroimaging studies of the Wisconsin card sorting task and component processes, *Hum Brain Mapp* **25**: 35–45, 2005.
31. Owen AM, McMillan KM, Laird AR, Bullmore E, The n-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies, *Hum Brain Mapp* **25**: 46–59, 2005.
32. Glahn DC, Ragland JD, Abramoff A, Barrett J, *et al.*, Beyond hypofrontality: A quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia, *Hum Brain Mapp* **25**: 60–69, 2005.
33. Price CJ, Moore CJ, Morton C, Laird AR, Meta-analysis of picture naming: The effect of baseline, *Hum Brain Mapp* **25**: 70–82, 2005.

34. Tan L-H, Laird AR, Fox PT, Neuroanatomical correlates of phonological processing of Chinese characters and alphabetic words: A meta-analysis, *Hum Brain Mapp* **25**: 83–91, 2005.
35. Bolger DJ, Perfetti CA, Schneider W, A cross-cultural effect revisited: Universal structures plus writing system variations, *Hum Brain Mapp* **25**: 92–104, 2005.
36. Brown S, Ingham RJ, Ingham JC, Laird AR, *et al.*, Stuttered and fluent speech production: An ALE meta-analysis of functional neuroimaging studies, *Hum Brain Mapp* **25**: 105–117, 2005.
37. Petacchi A, Laird AR, Bower JM, The cerebellum and auditory function. An ALE meta-analysis of functional neuroimaging studies, *Hum Brain Mapp* **25**: 118–128, 2005.
38. Farrell MJ, Laird AR, Egan GF, Brain activity associated with painfully hot stimuli applied to the upper limb: A meta-analysis, *Hum Brain Mapp* **25**: 129–139, 2005.
39. Grosbras M-H, Laird AR, Paus T, Cortical regions involved in gaze production, attention shifts and gaze perception, *Hum Brain Mapp* **25**: 140–154, 2005.
40. Stroop JR, Studies of interference in serial verbal reactions, *J Exp Psychol* **18**: 643–662, 1935.
41. Derrfuss J, Brass M, von Cramon DY, Cognitive control in the posterior frontolateral cortex: Evidence from common activations in task coordination, interference control, and working memory, *Neuroimage* **23**: 604–612, 2004.
42. Bomze IR, Pelillo M, Stix V, Approximating the maximum weight clique using replicator dynamics, *IEEE Trans Neural Netw* **11**: 1228–1241, 2000.
43. Fitzgerald PB, Oxley TJ, Laird AR, Kulkarni J, *et al.*, An analysis of functional neuroimaging studies of dorsolateral prefrontal cortical activity in depression, *Psych Res: Neuroimaging* **148**: 33–45, 2006.
44. McIntosh AR, Gonzalez-Lima F, Structural equation modeling and its application to network analysis in functional brain imaging, *Hum Brain Mapp* **2**: 2–22, 1994.
45. McIntosh AR, Gonzalez-Lima F, Structural modeling of functional neutral pathways mapped with 2-deoxyglucose: Effects of acoustic startle habituation on the auditory system, *Brain Res* **547**: 295–302, 1991.
46. Penny WD, Stephan KE, Mechelli A, Friston KJ, Modeling functional integration: A comparison of structural equation and dynamic causal models, *Neuroimage* **23**: S264–S274, 2004.
47. Friston KJ, Harrison L, Penny W, Dynamic causal modeling, *Neuro Image* **19**: 1273–1302, 2003.