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Resting-state fMRI data reflects default network activity rather than null data: A defense of commonly employed methods to correct for multiple comparisons

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ABSTRACT

Analysis of functional magnetic resonance imaging (fMRI) data typically involves over one hundred thousand independent statistical tests; therefore, it is necessary to correct for multiple comparisons to control familywise error. In a recent paper, Eklund, Nichols, and Knutsson used resting-state fMRI data to evaluate commonly employed methods to correct for multiple comparisons and reported unacceptable rates of familywise error. Eklund et al.'s analysis was based on the assumption that resting-state fMRI data reflect null data; however, their 'null data' actually reflected default network activity that inflated familywise error. As such, Eklund et al.'s results provide no basis to question the validity of the thousands of published fMRI studies that have corrected for multiple comparisons or the commonly employed methods to correct for multiple comparisons.

Functional magnetic resonance imaging (fMRI) is widely used to identify the brain regions associated with a cognitive process. Analysis of fMRI data typically involves over 100,000 independent statistical tests; therefore, it is necessary to correct for multiple comparisons to control familywise error and produce valid results. Eklund, Nichols, and Knutsson (2016) evaluated commonly employed methods to correct for multiple comparisons with physiological fMRI data rather than simulated fMRI data. Specifically, resting-state fMRI data from 499 participants were used to conduct 2,880,000 group analyses and compute the familywise error rates of the popular software packages SPM (Ashburner, 2012), AFNI (Cox, 1996), and FSL (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). Eklund et al. reported that, at individual voxel thresholds of $p < .01$ and $p < .001$, the rates of familywise error (i.e., false clusters of activity) were many times higher than the generally acceptable rate of 5%. If Eklund et al.'s findings were correct, they would question the validity of thousands of published fMRI studies that have corrected for multiple comparisons and commonly employed methods to correct for multiple comparisons. However, Eklund et al.'s analysis was based on the assumption that resting-state fMRI data reflect null data.

Resting-state periods produce fMRI activity in the default network, which has been associated with many cognitive processes including retrieval of personal information, planning for the future, day dreaming, mind wandering, and lapses of attention (for a review, see Buckner, Andrews-Hanna, & Schacter, 2008). The default network includes the dorsolateral prefrontal cortex, the medial prefrontal cortex, the inferior parietal cortex, and the medial parietal cortex (Figure 1a). Given that resting-state periods produce activity in the brain's default network, it is not surprising that the 'false clusters' reported by Eklund et al. occurred in default network regions (Figure 1b). These findings indicate that Eklund et al.'s assumption that resting-state fMRI data reflect null data is incorrect. As such, the large majority of 'false clusters' reported by Eklund et al. likely reflected true activations (i.e., true clusters) that inflated familywise error.

Null fMRI data should have a relatively uniform spatial distribution across the brain and should produce few, if any, significant activations. One way to create true null physiological fMRI data is to contrast odd versus even trials of one event type such that activity associated with that event is subtracted out leaving only physiological noise. For the present analysis, this was done using fMRI data from a recent
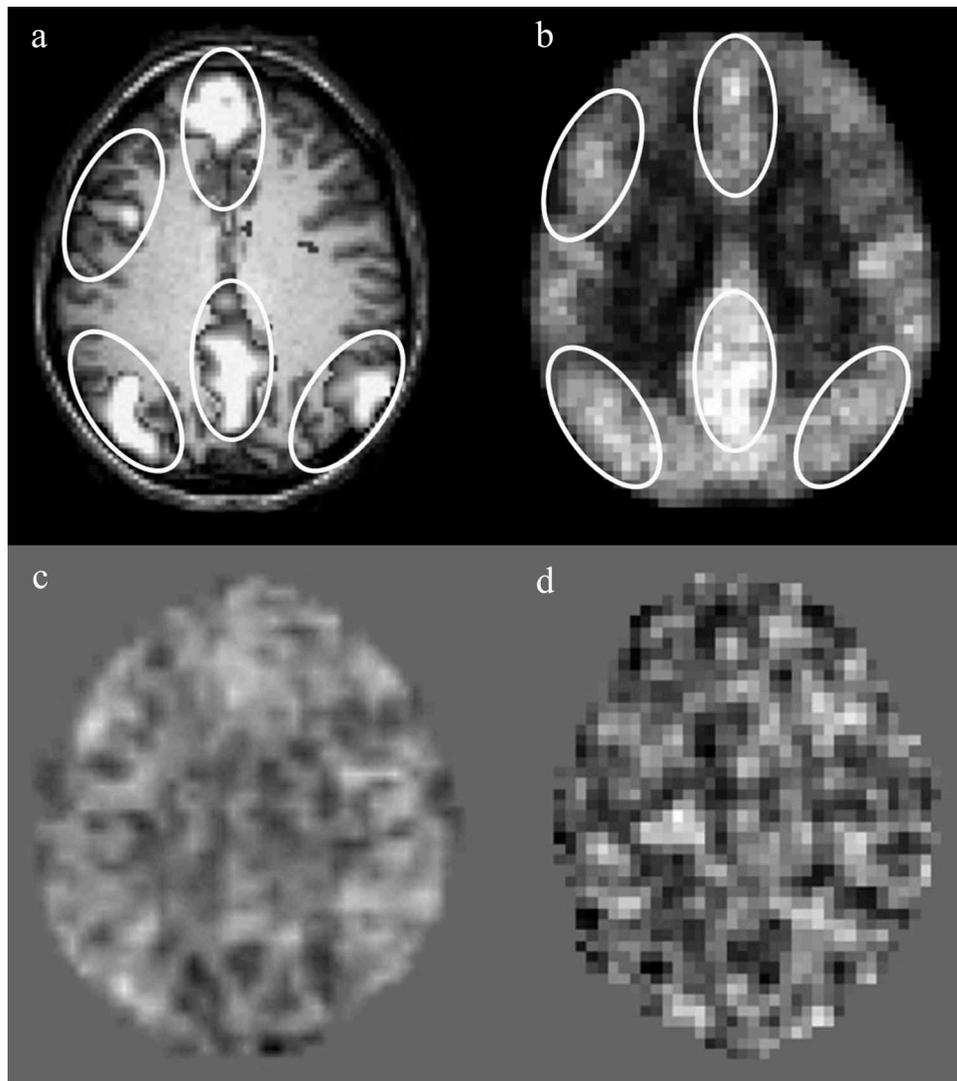
Figure 1. fMRI default network activity and null data. (a) Default network activity (within ovals; axial view, anterior toward the top; adapted from Figure 3 in NeuroImage, 37/4, Randy L. Buckner and Justin L. Vincent, Unrest at rest: Default activity and spontaneous network correlations, 1091–1096, 2007, with permission from Elsevier). (b) 'False clusters' from Eklund et al. in default network regions (within ovals; adapted from Supplementary Figure 18 in Eklund et al.). (c) Physiological null data. (d) Simulated null data.

spatial memory study (Jeye, Karanian, & Slotnick, 2016). During encoding, abstract shapes were presented to the right or left of fixation. During retrieval, shapes from encoding were presented at fixation, and participants identified each shape's previous spatial location. A random-effect general linear model analysis was conducted. As expected from null fMRI data, the contrast of odd versus even encoding-right trials produced activity that was relatively uniformly distributed across the brain (Figure 1c). Also as expected, this contrast did not produce any significant activations at an individual voxel threshold of $p < .001$, corrected for multiple comparisons to $p < .05$ by enforcing a minimum cluster extent of 10 voxels (the same pattern of results was obtained for encoding-left trials). This cluster size was determined using a script (cluster_-threshold_beta.m; Slotnick, n.d.) that ran 10,000 Monte Carlo simulations based on individual voxel and familywise p-values, contrast image spatial autocorrelation (4.54 mm), and volume parameters (Figure 1d illustrates one simulation; see Slotnick, Moo, Segal, & Hart, 2003). Of importance, in this script, clusters of activity can have any spatial configuration (i.e., they are not assumed to be Gaussian in shape). Note that it is simple to simulate realistic fMRI data (compare Figures 1c and 1d), rather than 'very hard' as claimed by Eklund et al. (p. 7900),

which is why methods to correct for multiple comparisons are typically evaluated using simulated null data.

The fact that the null physiological data in the present analysis did not produce any activation at $p < .001$ (cluster extent corrected to $p < .05$) is consistent with my experience analyzing fMRI data for nearly two decades. It is extremely rare to see activity in an unanticipated region using this threshold, which would occur often if it was too lenient. There is no question that the familywise error rate of 60–90% at $p < .001$ (enforcing a minimum cluster extent of 10 voxels) reported by Eklund et al. is highly inflated, which can be attributed to their 'null data' actually reflecting default network activity. It is anticipated that if true null physiological data had been employed, all the methods to correct for multiple comparisons would have produced acceptable rates of familywise error.

Eklund et al.'s analysis was based on the incorrect assumption that resting-state fMRI data reflect null data. As such, their findings provide no basis to question the validity of the thousands of published fMRI studies that have corrected for multiple comparisons or the commonly employed methods to correct for multiple comparisons.

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