Interclass Correlation Coefficient as a Measure of Drug Intervention in FMRI

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Introduction

Test-retest reliability is considered an important characteristic of measures used in repeated-measures designs such as longitudinal assessments or drug studies. Functional neuroimaging studies have indicated both good and poor reliability of activation patterns. For studies that utilised voxel-wise analysis of data, good reliability of voxels within activated regions has been demonstrated. However, acceptable reliability statistics also occur outside of activated regions as would be expected in any randomly-sampled data set. The aim of the present study was to understand the nature of the distribution of the reliability statistic across the entire brain volume as a function of the activation statistic, and the effects of pharmacological intervention on such a distribution. We utilised tasks of general interest in neuroimaging research to ensure widespread applicability of the analyses presented and use a learning task to illustrate our findings here. Even when liberal statistical thresholds are used areas considered significantly activated typically amount to around 10% of the brain volume suggesting that genuinely reliable activations will produce only subtle changes in the distribution of the reliability statistic across the entire brain volume as a function of the activation statistic. We hypothesised that as a function of the reliability static (1) the distribution of the number of voxels would be negatively skewed for voxels with higher activation statistic and (2) the introduction of a drug on one (random) session for each subject would decrease this skewness if the drug effect is larger than the inherent variability for the two sessions. Such analyses would allow description of the effects of a drug on the distribution of data within the entire brain volume, in addition to the standard analyses which focus on localised changes within specific regions.

Method

The task performed was based on the paired associated learning task from CANTAB (Owen et al., 1993). Six abstract patterns were displayed in a pseudo-random order around the screen (encoding). Afterwards, the same six patterns were shown in the centre of the screen one at a time; and participants indicated the location of each pattern using a joystick (retrieval). The encoding and retrieval stages were repeated two further times with identical patterns. A total of six sets of patterns were used to allow identification of brain networks involved in encoding and retrieval during learning. For the test-retest study, 10 young healthy male volunteers were scanned on two occasions. For the drug study 16 young healthy male volunteers were scanned on two occasions, once after placebo injection and once after injection of scopolamine 0.4mg (s.c.). Scopolamine was chosen as it produces marked impairments in learning and memory tasks and has been shown to alter BOLD signal during such tasks. SPM5 was used to analyse the data. Realignment of the time series was followed by co-registration to a high resolution image and normalisation. To reduce mapping errors, a single structural image for each subject was used in the co registration of both sessions. The data was not smoothed in order to keep the voxel measurements as independent as possible. This data was then fitted to the paradigm model and the parameter values corresponding to the difference between control and task encoding were obtained. Written as SPM5 contrast images for each subject and each session, this voxel dependent parameter was used to calculate the ICC maps for both test-restest and drug studies. T-statistics for the first test-retest session and placebo session where obtained as a measure of activation during memory encoding.

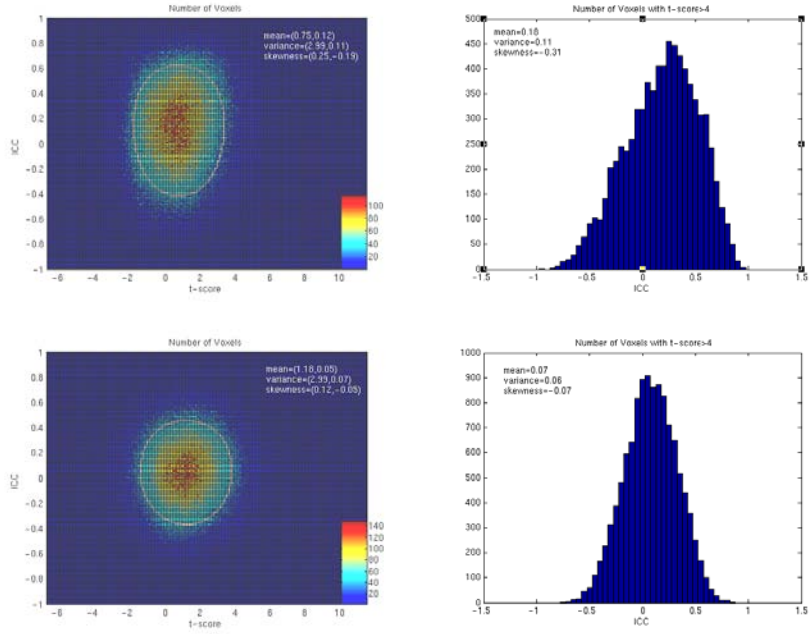

Figure 1: Histrograms of the number of voxels for a given ICC and t-statistic (left panels), limited to voxels above an t-statistic of 4.00 indicating probable activation (right panels). Test-retest data is shown on the upper panels and the effect of 0.4mg scopolamine (s.c.) on the lower panles.

Results

To explore the relationship between the ICC and t-score across the whole brain volume, we display the results as a 2D histogram. The left panels of Figure 1 show the number of voxels for a given ICC and t-score value for the test-retest and drug studies. If the ICC and t-score are not related then it is assumed their histogram can be obtained from standard distributed variables. Therefore any deviation from this behaviour can be considered as an indication of an ICC - t-score relationship. The left panels show an equal probability curve (white) arising from a bivariate standard distribution, transformed back to the ICC-t variables and centred in the mean values. The curve follows closely the equal probability profile of each histogram revealing a random sampling process of ICC and t-score across the brain. Because of these random characteristics, reliability can thus take high values for any degree of activation.

For the test-retest study we can see that for high t-scores negative values of ICC are less probable than positive ones. The mean value and the skewness toward high values of both ICC and t-score thus favour a mutually increasing relationship. A cumulative histogram with t>4 shows that the voxels in the activation network have a higher mean and a notable negative skew (shift to the right). In the drug study we confirm that the skewness was closer to zero, making the joint histogram closer to the standard distribution case. The mean ICC across the brain was also reduced.

Discussion

The ICC is a random variable and therefore simply extracting ICC for 'peak' activation voxels or regions of interest may not be sufficient to describe reliability characteristics of a functional imaging data set. Understanding subtle variations in ICC that may arise from performing cognitive tasks or after administration of a drug offers a refined perspective of the information that can be derived from the entire brain volume.

The test-retest statistic used here (ICC) had a skewed distribution from normal, particularly for voxels of higher activation. This reflected the expected influence of increased reliability for the regions that are involved in encoding of paired associates during the learning task. The mean ICC for the entire distribution was also greater than zero indicating task performance also influenced reliability across the whole brain. These measurable changes occurred despite the task activating only 5% of the voxels, demonstrating that task performance has effects beyond the voxels that are typically marked as 'activated'. The variance introduced by a drug reduced the skewness of the voxels showing higher activation, as hypothesised, demonstrating the widespread influence of scopolamine on the network of brain regions involved in encoding. In comparison, a standard interaction contrast between drug and placebo showed scopolamine to alter activity in a small region of the hippocampus (not shown here). Overall, the methodology presented utilises the reliability statistic to describe test-retest effects on the entire data set acquired and provide a novel perspective on the influence of a pharmacological agents on fMRI measures of task-related activity.

References

Owen, A.M. et al. *Brain*, 1992, 115, 1727-1751. Shrout, P.E. & Fleiss, J.L. *Psychological Buletin*, 1979, 86, 420-428

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