A novel approach to modeling state-related fMRI activity using change-point theory

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INTRODUCTION
Goal: To develop and apply a hybrid hypothesis- and data-driven analysis for modeling sustained psychological states with uncertain onset time and duration; e.g., experienced emotion, learning, insight.

Our approach: Uses ideas from statistical control theory and change point analysis
- Population inference on whether and when a time series changes from a baseline state
- Handles uncertain onset times and durations

Simulations: false-positive rate (FPR) control and power
Application: fMRI study (n = 25) of state anxiety.

Toolbox: Matlab implementation freely available
- http://www.columbia.edu/cu/psychology/tor/

METHODS
Our method is a multi-subject extension of the exponentially weighted moving average (EWMA) method used in change-point analysis. The analysis uses activity collected during a baseline period to estimate noise characteristics in the signal, and then makes inferences on whether, when, and for how long subsequent activity deviates from the baseline level. We extend existing EWMA models for individual subjects (a single time series) so that they are applicable to fMRI data, and develop a group analysis using a hierarchical model, which we term HEWMA (Hierarchical EWMA). The HEWMA method can be used to analyze fMRI data voxel-wise throughout the brain, data from regions of interest, or temporal components extracted using ICA or similar methods.

Detecting Change points
- No a priori assumptions about the nature of changes in the fMRI signal. Can handle activation or deactivation, short or prolonged activation duration.
- EWMA is a search for activity differences across time, correcting for multiple dependent comparisons tested

EWMA
- Given observations in time \[X = (x_1, x_2, ... , x_T)\]
- Two-state model: baseline ("in-control") and activated ("out-of-control"). Assumed that \(X\) is distributed normally: \(N(0, 1)\) for baseline and \(N(\theta, \sigma)\) for activated.
- \(\theta_i\) is estimated from pre-specified baseline period
- After baseline, process is "in control" up to some unknown time \(t\), the change point (CP), when the state changes to activated (see Fig. 1).
- The exponentially weighted moving-average (EWMA) statistic, \(T_i\), is a temporally smoothed version of the data, which is defined as:

\[
z_i = \frac{x_i - \theta}{\sqrt{\sigma}}
\]

where \(\text{Var}(x_i)\) is a constant smoothing parameter chosen by the analyst (small \(\lambda\) gives more smoothing), and the starting value \(z_0\) is set equal to the baseline estimate of \(\theta_0\).
- To test whether the process has changed states at time \(t\), we compute a test statistic for each time point following the baseline:

\[
T_i = \frac{z_i - \theta}{\sqrt{\sigma z^2_i}}
\]

where \(\text{Var}(z_i)\) is the (co-)variance of the EWMA statistic at time \(t\).

- Theoretical results for \(T_i\) for a variety of noise models is provided in Lindquist and Wager (2006).
- Under the null hypothesis \(T\) follows a t-distribution.
- Family-wise error rate control across the time series is provided using Monte Carlo integration.

EWMA
- Generates null hypothesis data with covariance given by \[\text{Var}(x_i)\]
- Save the maximum absolute value obtained across the time series
- Compare observed activity using change-point technique

EWMA: A hierarchical extension of EWMA
- There is interest in fMRI in population inference
- Approach: EWMA for each subject; mixed-effects (hierarchical) test of significance across subjects at 2nd level
- Suppose the EWMA statistic at time \(t\) for subject \(i\), which we denote \(z_i^t\), is defined as in Eq. 1. The HEWMA statistic is a weighted average of the individual EWMA statistics, with the weights inversely proportional to the total variance for each subject, i.e.,

\[
\frac{\sum_{i=1}^{N} \frac{1}{\text{Var}(z_i^t)}}{\sum_{i=1}^{N} \text{Var}(z_i^t)}
\]

where \(x_i^t = z_i^t + \frac{1}{\text{Var}(z_i^t)}\). Here \(z_i^t\) is the variance from the single subject EWMA analysis and \(z_i^t\) is the between subject variance, known up to a scaling parameter \(\alpha\).

- Estimate using a restricted maximum likelihood (REML) approach
- Iterative estimation of \(\alpha\) and its variance components.
- The final step in the HEWMA framework is performing a Monte Carlo simulation to get corrected p-values, except here we use \(Z_{0,i}\) and its covariance matrix in the simulation.

Estimating Change points (CPs)
If a systematic deviation from baseline is detected, we estimate the time of change and recovery time (if any).
- Zero-crossing method: use the last time point at which the process crosses \(\theta_i\) before becoming significant. Run duration: number of contiguous activated time points.
- MLE method: maximum likelihood estimates of \(t\)
- Gaussian mixture model method: 2-state (control and activated); classify time points in one of the two states. Estimate duration of activated runs as above.

Clustering into regions
- A natural unit of analysis is a multi-voxel region whose voxels show similar properties. We first obtain a Change Point Map (CPM) and Activation Duration Map over all significantly activated voxels.
- \(K\)-means clustering in 2-D (CP and duration) space.
- Number of classes chosen based on histogram (Fig. 4).
- Contiguous voxels of same class are "regions"

Simulations
- Assess the FPR and power for the HEWMA method (\(N = 20\))
- \(\tau\) = 0.8 (Sim 1: 0.1, 0.3, 0.5, 0.7 and 0.9) and duration of the baseline period (Sim 2: 20, 40, 60 or 80 time points).
- Error models in EWMA estimation: white noise (WN), AR(1), AR(2) and ARMA(1,1).
- \(N = 20\) subjects, \(\text{Var}(z_i) = 0.33 \times \text{Var}(x_i)\), 5000 replications
- FPR simulation: null hypothesis data with no activation was created using actual fMRI noise time courses.

Power simulation: As above, with active period of length 50 time points was added to noise data, Cohen’s d of 0.5.

Experimental design
24 participants were scanned in a 3T GE magnet. Participants were informed that they were to be given two minutes to prepare a seven-minute speech, and that the topic would be revealed to them during scanning. They were told that after the scanning session, they would deliver the speech to a panel of expert judges, though there was “a small chance” that they would be randomly selected not to give the speech. After the start of acquisition, participants viewed a fixation cross for 20 s (resting baseline). At the end of this period, participants viewed an instruction slide for 15 s that described the speech topic, which was to speak about “why you are a good friend.” The slide instructed participants to be sure to prepare enough for the entire 7 min period. After 2 min of silent preparation, another instruction screen appeared (a “relief” instruction, 15 s duration) that informed participants that they would not have to give the speech. An additional 2 min period of resting baseline followed, which completed the functional run (Fig. 5). During a run, a series of 215 images were acquired (TR = 2s).

RESULTS
Simulations of group data showed that false positive rates were adequately controlled for all noise models. The HEWMA analysis on the experimental data revealed task-related changes consistent with previous literature, including activations in dorsolateral and rostral medial prefrontal cortices, medial temporal gyrus, and occipital cortex (Figs. 4 and 5). Deactivations were found in ventral striatum and ventral anterior insula. \(K\)-means classification of voxels by activation onset time and duration revealed distinct patterns of responses to the task (color-coded by class in Fig. 4). Time courses for two patterns of responses are shown in Fig. 5, including a medial prefrontal region showing sustained activity throughout the anxiogenic task and an occipital region showing transient responses to the instruction periods (when visual stimuli were presented).

REFERENCES