Meta-analysis of functional Magnetic Resonance Imaging (fMRI)

Coordinate-based meta-analysis is a popular method for fMRI, these toolboxes have been developed:
- Activation Likelihood Estimation (ALE) [2,3]
- Multi-level Kernel Density Analysis (MKDA) [6]
- Seed-based d Mapping [12] (uses peak height as effect size when available)

Meta-analyses require publication bias diagnostics
- Publication bias: studies that fail to show significance in a certain region fail to get published
- This study introduces publication bias measures for coordinate-based meta-analysis methods that do not rely on effect sizes (e.g. ALE)

### Results and discussion

1. Fail-Safe N [30] (test for % contributing studies)
   - How many null studies can be added to a meta-analysis showing a significant effect in a region before the result is no longer statistically significant?

   **Simulation study**
   - 3 ‘real’ studies with 1 peak in target region distance on average 3mm from location true activation
   - Null studies each 1 peak in quadrant 2,3 or 4
   - Effect of sample size: small (n~10), medium (n~20) or large (n~30), se=1
   - Effect of thresholding: 7 thresholding methods

2. Regression test for sample size of contributing studies [30]
   - Verifies whether the resulting clusters of a meta-analysis are caused by activation foci stemming from small studies (small sample bias).

   **How does it work?**
   - Sleuth database was searched for experiments with paradigm class ‘taste’.
   - Contrast taste > no taste was selected (87 studies, 529 foci).
   - Voxsel FWE < 0.05 thresholding resulted in 4 statistically significant clusters.
   - Two of these clusters are plotted below and checked for a small sample bias.

   **This meta-analysis is conducted solely for demonstration, references on request.**

   **Introduction of 2 methods for the assessment of publication bias:**

   1. **Fail-Safe N**
      - Big influence of both thresholding method and sample size
      - A lot of variability within conditions
      - What is an acceptable number of null studies that can be added without altering the results?
      - Too low? Points at non-robust results. (In spirit of classic Fail-Safe N [30])
      - Too high? One or a small number of studies drives the entire analysis
      - Results for sample size: contra-intuitive for robustness but intuitive for leniency
      - Uncorrected thresholding shows large influence of small number of studies [30]

   2. **Regression test for sample size of contributing studies**
      - Given a significant ALE cluster,
        - included studies get a value of 0 (did not contribute to cluster) or 1 (contributed to cluster)
        - activation (x-axis) is plotted against sample size (y-axis)
        - slope gives an indication about publication bias

   **Results and discussion**

   - Results indicate a small sample bias for the first cluster, not for the second.
   - Effect of thresholding at study level?

   **Graphs of clustering methods**

   **Figure 1:** Overview of ALE meta-analysis.

   **Figure 2:** The brain is divided in 4 quadrants for simulations, true activation at the location of the yellow dot.

   **Figure 3:** Amount of null studies that can be added to a meta-analysis of 3 studies before the target cluster is no longer statistically significant, by thresholding method and average sample size.

   **Figure 4:** Two significant clusters and a selection of studies, their sample sizes and whether they have foci that contributed to the clusters.

   **Figure 5:** Possible patterns based on presence or absence of publication bias.

   **Figure 6:** Regression test results for each of the two depicted clusters.