- Statistic image: effect on interest evaluated at each voxel →Can lead to a parametric map.
- Without a priori assumptions, the entire statistical image has to be assessed. but using such a method that accounts for multiplicity in testing multiple voxels at once.
        - Enter the parametric statistical framework, where data is assumed to be normally distributed.
        - Nonparametric tests: deals with the multiple comparisons issue.
- Classic parametric statistical framework:
- "Applications of permutation testing methods to single subject *f*MRI require modelling the temporal auto-correlation in the
- time series"

- Aims: "The aim of this study is to make the multiple comparisons nonparametric permutation approach of
- Holmes et al. (1996) more accessible, complement the earlier formal exposition with more practical considerations, and illustrate the potential power and flexibility of the approach through worked examples"

- Randomization tests and permutation tests lead to the exact same results.
    - Randomization: Label scans as A or B, according to the scanning condition.
    - Null Hypothesis: I the above example, null == scans are the same, no matter the condition. If the conditions were presented in a different order, there would still be the same results regardless. ➔ Data is fixed, design is random.
        - Thus, since the labeling is arbitrary, labels may be re-randomized ➔ permuting the labels.
    - Exchangeability: To be done before data collection, but after condition labels have been assigned.
        - Labels on the to-be-collected data are exchangeable if the statistic distribution is the same whatever the labeling.
        - Continuing from the example above: Active and baseline scans according to the null hypothesis would be no difference. Permutation distribution is the sampling distribution of the statistic under the null hypothesis.
- Permutation Test
    - May be impractical to randomly allocate experimental conditions. Or there is data from an experiment that is not randomized. (seeking brain regions whose activity is possibly related to covariate value)
        - Justification for permutations:
            - distributions have the same shape, or are symmetric.
            - degree of exchangeability must be assumed post-hoc.
- Single Voxel Example
    - 3 scans in Active cond. (A), and 3 in Baseline cond. (B),
        - Calculate the mean difference in the voxel for the different scans of the conditions.
    - Randomization test
        - simple randomization of all 6 scan, leads to 20 possible labeling schemes. (AAABBB; AABABB, etc.)

    - Permutation test
        - If ABABAB was chosen, assume that the voxel values are the same, except possible difference in location or mean.
- Multiple Comparisons Permutation test
    - For each voxel a test can be performed. A priori assumptions of brain region can be tested, or if no region is assumed beforehand, a effect must be assessed at each voxel.
    - Single threshold
        - voxels whose statistical values exceeding a “critical threshold” will have their null hypothesis rejected. Permutation distribution of the statistic as
    - Suprathreshold cluster
        - assesses a pattern of suprathreshold activity at a predetermined primary threshold. Size of connected suprathreshold regions for significance are determined.
            - these tests are useful for connectivity, but additional power, but at a price of reduced localizing power.
- The key steps of doing a permutation analysis:

1. *Null Hypothesis*
   Specify the null hypothesis.
2. *Exchangeability*
   Specify exchangeability of observations under the null hypothesis.
3. *Statistic*
   Specify the statistic of interest, usually broken down into specifying a voxel-level statistic and a summary statistic.
4. *Relabeling*
   Determine all possible relabeling given the exchangeability scheme under the null hypothesis.
5. *Permutation Distribution*
   Calculate the value of the statistic for each relabeling, building the permutation distribution.
6. *Significance*
   Use the permutation distribution to determine significance of correct labeling and threshold for statistic image.

- Parametric Design: Test data: one subject, scanned 12 times, presented with brief auditory stimuli, a score was computed for each scan to, according to the amount of activity infused into the brain during stimulation.
    - Scan score is the covariate of interest (DURATION), global cerebral blood flow is a nuiscance covariate.
        - Null hyp. assumptions➔ “The data would be the same whatever the DURATION”
        - Exchangability: the experiment was randomized, values of duration were grouped into three blocks.
        - Statistics: Clusters are defined by suprathreshold voxels.

        - Enumeration: 24 ways to permute 4 labels (4X3X2X1), and each block is randomized, so 13,824 possible permutations of labels. Becausethis takes forever, a smaller sample (1000) was chosen.
    - Results: suprathreshold cluster lager than 462 (95th percentile) are deemed significant.
    - Discussion
- Multi-subject PET: Activation: Study: standard repeated measures t-statistic; data: randomly placed rectangles (baseline: pattern was stationary; active: rectangles moved smoothly in opposite directions), 12 subjects placed randomly in one of two scan conditions
    - Null: Each subject would have the same results even if the conditions were switched.
    - Statistic: Must use a random effects model to account for subject differences.
    - Summary: this example shows the shows the role of the permutation test of evaluating other procedures.
- Multi-subject fMRI: Activation: done to make an inference on a population. Study: 12 subjects, 8 fMRI acquisitions; two possible presentation orders for each block, randomization across blocks and subjects. TR= 2 s, 528 scans per condition. Item recognition and control were the conditions.
    - To generalize a population we need a permutation test.
    - Because fMRI studies usually have fewer than 20 participants, using the permutation test yielded more robust results than the t-statistic, due to the method being more sensitive to picking up voxel activity.
- Comparisons between parametric and nonparametric test results must be made very carefully. Multiple comparisons problem can be accounted for, and only a minimal amount of assumptions need to be made, to get an accurate inference. Nonparametric tests can be used to assess the validity of parametric tests

Important to stick to the steps of the permutation test.