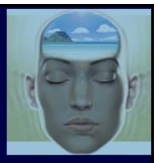
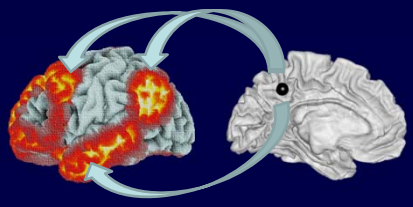
Seed Driven 'Resting State' Functional Connectivity





Susan Whitfield-Gabrieli
MIT

Outline

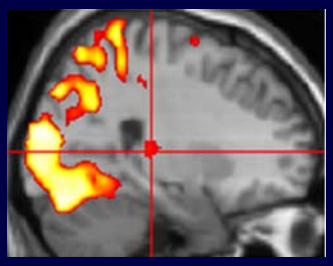
- Seed driven resting state functional connectivity: rs-fcMRI
- Treatment of noise
- Current debates in the field (respiration/anticorrelations)
- Compcor method /Anticorrelation experiment
- Motion and Artifacts
- Introduction to functional conn toolbox

Structure – Function Relationships

Functional *Segregation*

- Univariate analyses of regionally specific effects

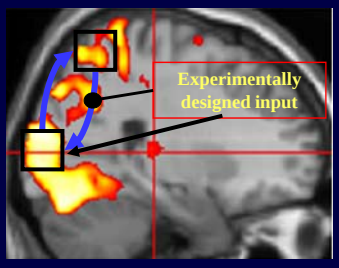
Identification of local regions that are specialized for a particular task



Functional *integration*

- Multivariate analyses of regional interactions

Identification of interactions between regions that allow integrated function



SPM

Functional integration
subdivided into:

Functional connectivity

= the temporal correlation between spatially remote areas

MODEL-FREE

Exploratory

Data Driven

No Causation

Whole brain connectivity

Effective connectivity

= the influence one area exerts over another

MODEL-DEPENDENT

Confirmatory

Hypothesis driven

Causal directions

Reduced set of regions

Connectivity Analysis Methods

- ***Functional Connectivity***

  - PCA/ICA (principal/independent component analyses)
  - Pairwise ROI Correlations
  - **Seed driven connectivity ****

  Estimates maps showing temporal correlations between the BOLD signal from a given seed and that at every brain voxel

  - Graph analyses

- ***Effective Connectivity***

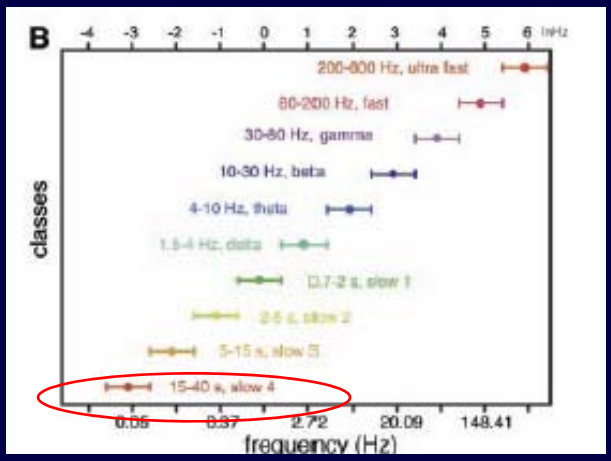
  - PPI (psycho-physiological interactions)
  - SEM (structural equation models)
  - MAR (multivariate autoregressive models)
  - Granger Causality
  - DCM (dynamic causal models)

Resting State Networks

Spontaneous, low-frequency fluctuations in the fMRI BOLD that exhibit specific networks of the human brain in the absence of over task.

(Biswal 1995, Lowe 2000, ,Greicius 2003, Fox 2005)

Frequency Bands



[.025 .06], toolbox cutoff [.009 .08]

Buzsaki , Science 2004

Resting State Network Characteristics

- Low Frequency (< .1 Hz)
- Reliable, robust and exists in infants, anesthesia, primates
- Task-independent: Relevant for understanding clinical & pediatric populations (bypass ceiling, floor & practice effects)
- Allows exploration of individual differences (e.g., Predict clinical outcome: identify which patients will respond to which treatments -Used as surrogate outcome measure for drug development or assessment of interventions)
- Easy to acquire and share data (Biswal in press PNAS, NYU)

(Large data sets can provide quantitative phenotypes for molecular genetic studies and biomarkers of developmental and pathological processes in the brain)

rs –fcMRI Applications

Resting state functional connectivity can reveal intrinsic, spontaneous networks which can help us understand the basic functional organization of the brain:

a) Used to illustrate that the brain is intrinsically organized into dynamic "anticorrelated" functional networks (Fox 2005)

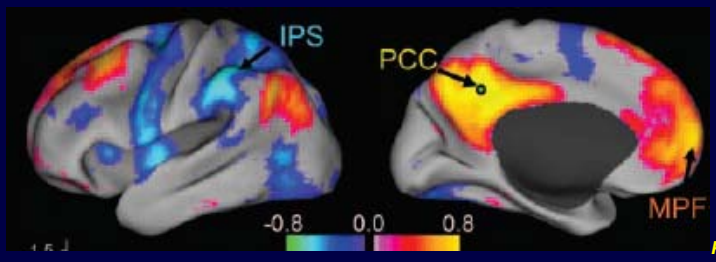
b) ROIs based on correlations in spontaneous fluctuations of the BOLD signal can predict localization of task-related functional responses. (Vincent et al 2006).

c) Used to functionally dissociate functionally and anatomically herterogeneous regions of interest (Margulies 2007 (ACC) , Roy 2009 (Amygdala))

d) Used to delineate functional topography of the brain: sharp transitions in correlation patterns may be used to determine functional boundaries across cortex (Cohen 2008).

Seed driven functional connectivity

Estimates maps showing temporal correlations between the BOLD signal from a given seed and that at every brain voxel



Fox PNAS 2005

e.g.
Fox et al., 2005. Proc. Natl. Acad. Sci. 102:9673–9678
Vincent et al, 2006 J Neurophysiol 96:3517–3531
Whitfield-Gabrieli et al, 2009, Proc. Natl. Acad. Sci. 102:9673–9678

Default Network

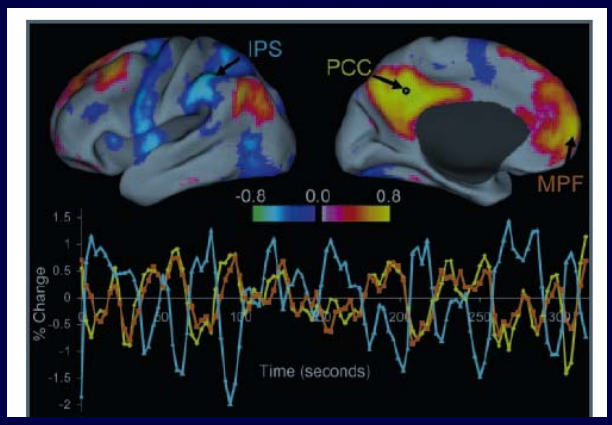
The default network is hypothesized to mediate task-independent or intrinsic thought rather than task-dependent extrinsic stimulus processing

Default Network

- In the healthy brain, greater suppression of the default network is associated with:
  - Better memory formation ***Daselaar, Neuroimage, 2004***
  - Increased task difficulty ***McKiernan, J Cogn Neurosci, 2003***
  - Fewer lapses of attention ***Weissman, Nat Neurosci , 2006***
  - Better learning of a cognitive skill /Less mind wandering ***Mason, Science, 2007***

So in general, the more these regions are suppressed, the better one can focus on the external world and the better one can perform the task.

Seed driven rs-fcMRI reveal default AND task related networks



Time courses: Correlated:PCC (yellow), MPFC (orange)
Anticorrelated: IPS (blue)

Fox et al., 2005. Proc. Natl. Acad. Sci. 102:9673–967

MPFC/DLPFC Anticorrelation

may reflect push/pull relationship between DMN/TPN

Internal (DMN,MPFC) *External (TPN,DLFPC)*

Engaged in…

- *self reflection*
- *future planning & past recollections*

- *external perceptions*
- *keeping task relevant information in mind (WM)*

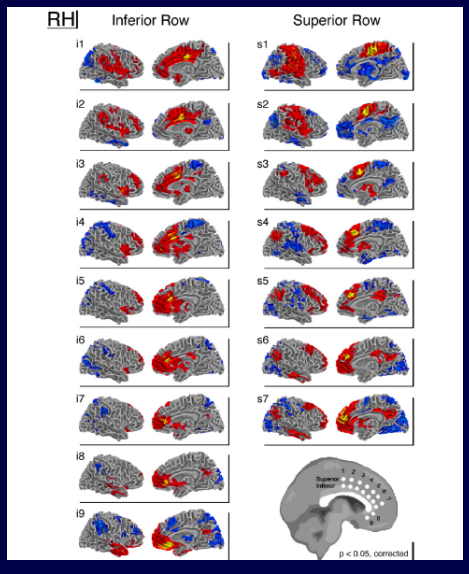
Magnitude of Anticorrelations may reflect ability to switch between Internal & External Processing Modes

Whitfield-Gabrieli & Ford 2012

Connectivity Maps Depend on Seed Location:

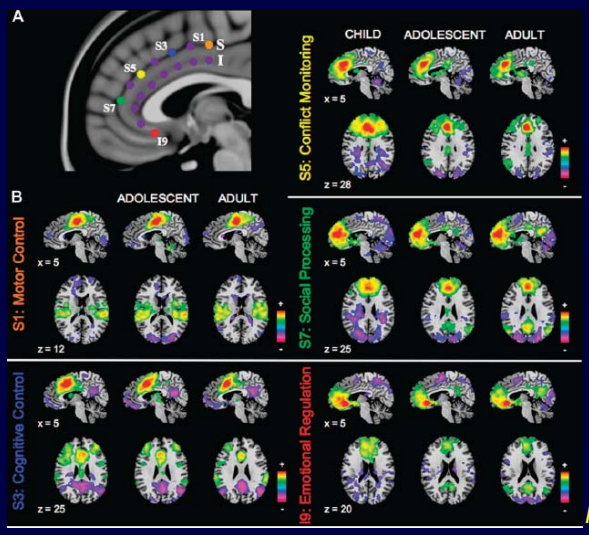
Flaw or Feature?

Functional segregation of ACC using seeded connectivity maps



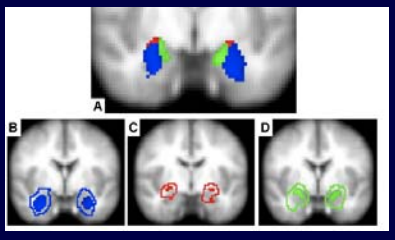
Margulies 2007

Development of ACC fc from childhood to adulthood

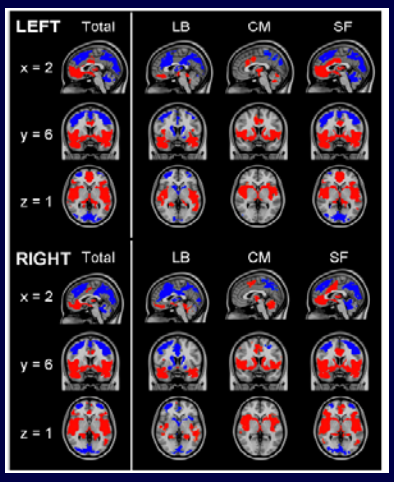


Kelly et al 2009

Functional segregation of Amygdala



LB: laterobasal
CM: centromedial
SF: superficial



Roy 2009

rs-fcMRI used to used to determine functional boundaries across cortex

ELSEVIER

NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 41 (2008) 45–57

Defining functional areas in individual human brains using resting functional connectivity MRI ☆

Alexander L. Cohen,[a,*] Damien A. Fair,[a] Nico U.F. Dosenbach,[b] Francis M. Miezin,[a,b] Donna Dierker,[c] David C. Van Essen,[c] Bradley L. Schlaggar,[a,b,c,d] and Steven E. Petersen[a,b,c,e,*]

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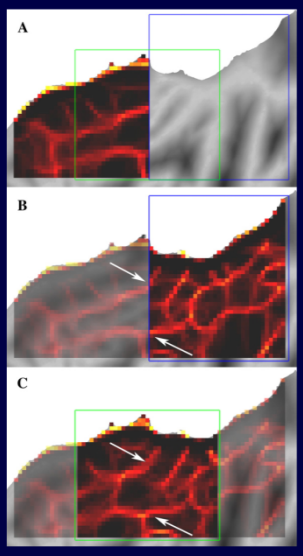
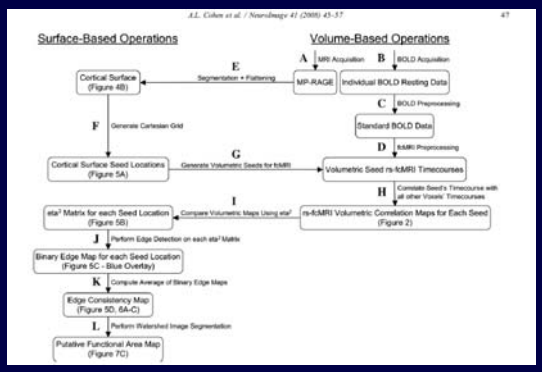
[d]*Department of Pediatrics, Washington University School of Medicine, St. Louis, MO 63110, USA*
[e]*Department of Psychology, Washington University School of Medicine, St. Louis, MO 63130, USA*

Received 24 September 2007; revised 8 December 2007; accepted 24 January 2008
Available online 25 March 2008

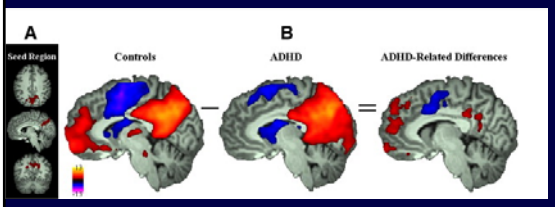
Cohen 2008





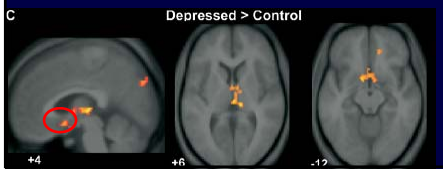
Sharp transitions in rs-fcMRI patterns were used to determine functional boundaries, reliably on individual and group data.

Clinical Characterization



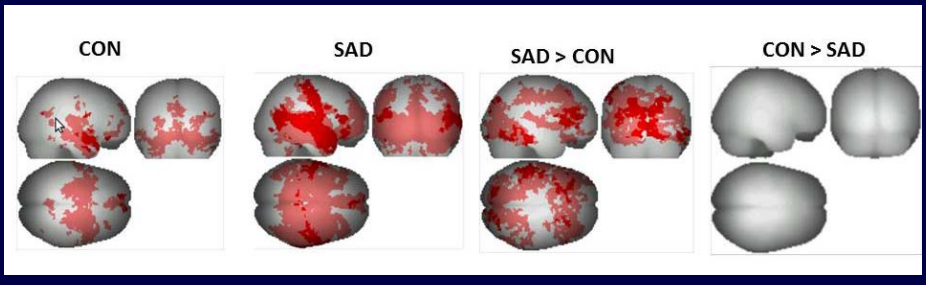
Cingulate-Precuneus Interactions:
A New Locus of Dysfunction in ADHD:
ADHD decreases in Precuneus/ACC Connectivity. Also, ADHD decreases in connectivity among precuneus and other default network components
Castellanos 2008

Increased default connectivity in *schizophrenia*, correlates with psychopathology
Whitfield-Gabrieli, PNAS 2009



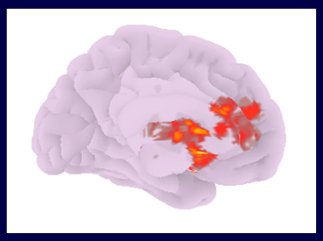
Increased default functional connectivity in patients with major depression
*subgenual ACC
Greicius, Biological Psychiatry, 2007

Clinical Prediction
Resting State HyperConnectivity with Amygdala

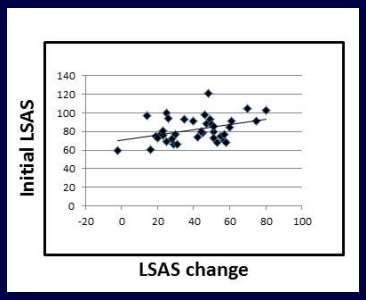


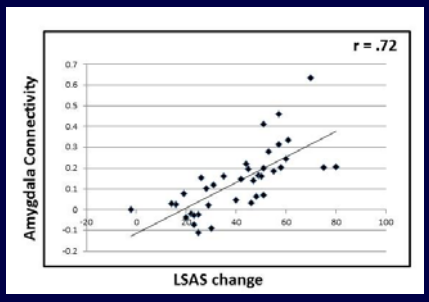
Whitfield-Gabrieli, 2013, *in prep*

Resting State Connectivity in SAD Predicts CBT Response



Better than current clinical scales





Whitfield-Gabrieli, 2013, *in prep*

Messages

- Resting state functional connectivity, which elucidates the intrinsic functional architecture of the human brain, is a very powerful method to investigate individual differences, as well as developmental, aging and clinical populations. It also holds great promise for clinical translation.
- ***However there are *critical* methodological issues that should be addressed in order to assure valid results (e.g., artifacts, global signal regression)***

Outline

- Seed driven functional connectivity
- Resting state seed driven functional connectivity: rs-fcMRI
- Treatment of noise
- Current debates in the field (respiration/anticorrelations)
- Compcor method
- Introduction to functional conn toolbox

BOLD noise in connectivity analyses

Non-neuronal contributions to BOLD signal

Noise sources

- Physiological noise
- Scanner drift
- Subject motion

In "activation" studies

Nuisance effects

Usually degrade power (lower statistical significance of the results)

In "connectivity" studies

Confounding effects

Introduce bias in results (show apparent connectivity between unrelated areas)

Need to appropriately characterize and remove noise effects to improve the validity of connectivity analyses

Low freq rs-fcMRI - Respiration?

ELSEVIER

NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 31 (2006) 1536 – 1548

Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI

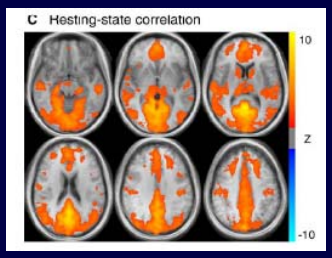
Rasmus M. Birn,* Jason B. Diamond, Monica A. Smith, and Peter A. Bandettini

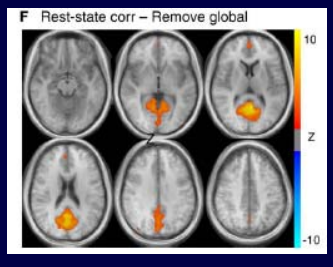
Laboratory of Brain and Cognition, National Institute of Mental Health, NIH, 10 Center Dr., Bldg. 10, Rm. 1D80 Bethesda, MD 20892-1148, USA

Received 26 August 2005; revised 9 January 2006; accepted 16 February 2006
Available online 24 April 2006

Removing Global Signal

The natural variation in breathing depth and rate during rest has a significant impact on rs-fcMRI analyses as the induced fMRI signal changes can occur at similar spatial locations and temporal frequencies.

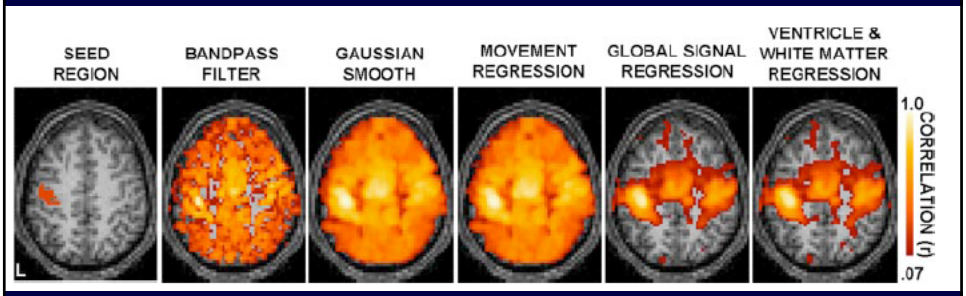




The global (whole brain) signal correlates with respiration-induced fMRI signal fluctuations

Birn 2006

Correlation processing steps



1) BPF Data: (.009<f<.08Hz) reduce effect of low freq drift and high freq noise
2) Gaussian spatial smooth (6mm FWHM)
3) Removal by regression of
   a) movement
   b) mean global signal
   c) mean ventricle
   d) mean white matter

Note: Each successive step increases the sensitivity and specificity of the correlations!!

Vincent et al 2006

Consequences of Removing Global Signal

Consequence of removing the global signal: The distribution of correlation coefficients throughout the brain is shifted such that there are roughly equal numbers of positive and negative correlations.

→ Anticorrelations are an "artifactual" consequence of global regression.

Anticorrelations - artifacts?

NeuroImage 44 (2009) 893–905

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

The impact of global signal regression on resting state correlations: Are anti-correlated networks introduced?

Kevin Murphy [a], Rasmus M. Birn [a], Daniel A. Handwerker [a], Tyler B. Jones [a], Peter A. Bandettini [a,b,*]

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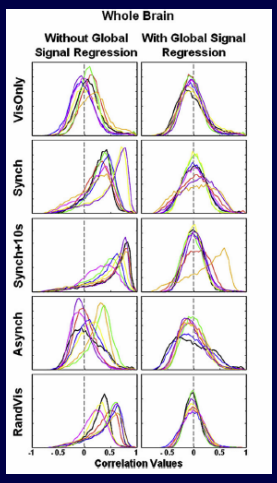
ABSTRACT

Low-frequency fluctuations in fMRI signal have been used to map several consistent resting state networks in the brain. Using the posterior cingulate cortex as a seed region, functional connectivity analyses have found not only positive correlations in the default mode network but negative correlations in another resting state network related to attentional processes. The interpretation is that the human brain is intrinsically organized into dynamic, anti-correlated functional networks. Global variations of the BOLD signal are often considered nuisance effects and are commonly removed using a general linear model (GLM) technique. This global signal

After global signal regression, the sum of correlation values with a seed voxel across the entire brain is less than or equal to zero.

$$\sum_{j=2}^{N} cc\left(x_1(t), x_j(t)\right) \leq 0.$$



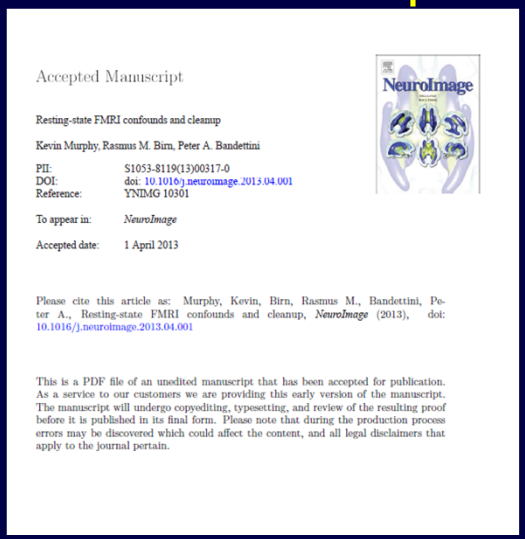
Murphy et al Neuroimage, 2009

Anticorrelations - artifacts?

The Global Signal and Observed Anticorrelated Resting State Brain Networks
Fox et al. *J Neurophysiol.* 2009; 101: 3270-3283

Correlations and anticorrelations in resting-state functional connectivity MRI: A quantitatige comparison of preprocessing strategies
Weissenbacher et al. *Neuroimage*, 2009

Resting State fMRI confounds and cleanup



Accepted Manuscript

Resting-state FMRI confounds and cleanup

Kevin Murphy, Rasmus M. Birn, Peter A. Bandettini

PII: S1053-8119(13)00317-0
DOI: doi: 10.1016/j.neuroimage.2013.04.001
Reference: YNIMG 10301

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This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Murphy et al., 2013

BOLD noise treatment in connectivity analyses

CompCor Approach (Behzadi et al 2007. *NeuroImage* 37 90–101)

Noise effects are not distributed homogenously across the brain (e.g. cardiac effects are particularly visible near vessels, respiratory effects appear more globally and stronger near edges in the image).

Compared to previous methods that subtract global signal across the brain and the mean signals from noise ROIs, the CompCor method is more flexible in its characterization of noise. It models the influence of noise as a **voxel-specific** linear combination of multiple empirically-estimated noise sources.

CompCor : Principal components (PCA) are derived from noise ROIS. These components are then included as nuisance parameters within general linear models.

Anticorrelation Study

In this study, we examined the correlations and anit-correlations in resting state connectivity with several different methods for the treatment of possible confounds.

Resting state data: ***One resting state scan of 10 minutes was collected*** in 14 healthy subjects. TR = 2.5s. 42 slices

Data preprocessing: ***Functional images were slice-time corrected,*** realigned, normalized and smoothed with a 6mm kernel in SPM5. Individual anatomical images were segmented to extract white matter and CSF masks.

Seed : ***MPFC (Fox et al., 2005). 10mm sphere centered at (-1, 47 -4).***

Correction for physiological and other noise sources:
Residual motion was regressed out in all three methods.
A temporal band-pass filter of .009 to .08 Hz was applied.

Resting fMRI BOLD time series

Preprocessing: realign, coregistration, normalize, smoothing

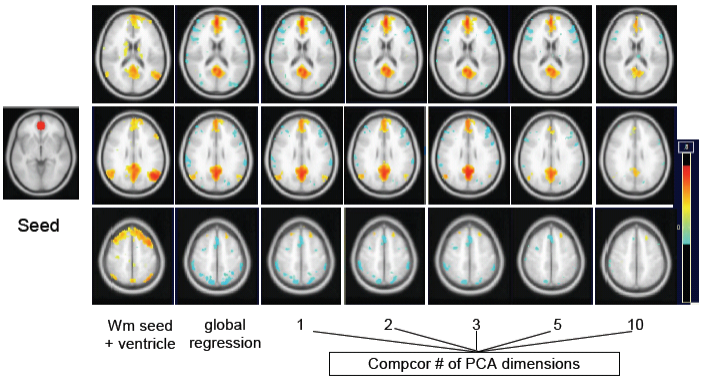
"Standard"	CONN
Whole brain regression (WB-reg) • ***Global signal*** regressed out • Regressed out WM and CSF • Head motion parameters regressed out. • Temporal band-pass filtering	**Compcor noise correction** **• WM, CSF masks segmented from anatomical image. Partial volume correction applied. (erosion)** **• Principal components of signal from WM, CSF masks regressed out.** • Head motion parameters regressed out. • Temporal band-pass filtering

Correlation analysis between the seed time series to whole-brain voxel time series

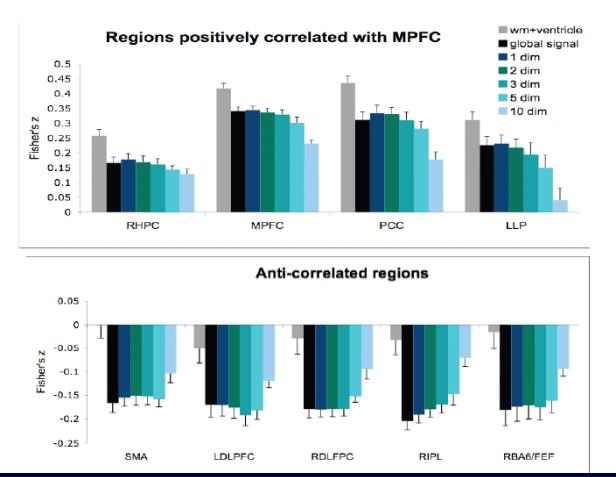
Chai et al., 2011

Connectivity with MPFC

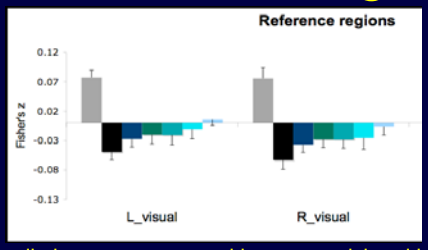
Correlation maps of the MPFC seed from different noise treatment approaches (p<.001, uncorrected).



Correlations / Anticorrelations



Reference Regions

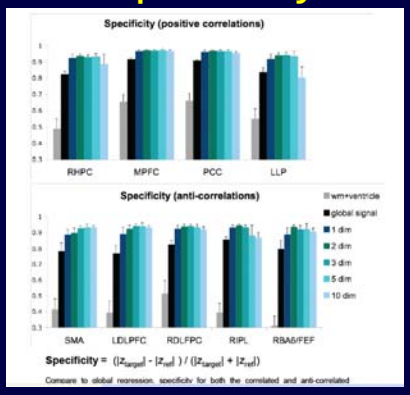


Wm+ventricle: does not eliminate apparent positive connectivity with reference regions (too small correction, there are other confounding effects not accounted for by the wm+ventricle average timeseries)

Global signal: introduces apparent negative connectivity with reference regions (too much correction, global signal correction forces the average connectivity to be approximately ze

Compcor: Increasing dimensions reduce the size of the apparent connectivity with reference regions. (intermediate solution, expands on the wm+ventricle method by adding increasing complexity to the characterization of noise within these ROIs without imposing artificial constraints on the expected distribution of connectivity values)

Specificity:



Compared to global regression, specificity for both the correlated and anti-correlated regions were improved when Compcor was used for noise-reduction.

Specificity = (|*ztarget*| - |*zref*|) / (|*ztarget*| + |*zref*|)

This quantifies to what extent each method is reducing the effect size in the areas of interest (decreasing sensitivity) compared to how much each method is reducing the effect size in the reference areas (increasing validity)..

Specificity: Weissenbacher, Neuroimage, 2009

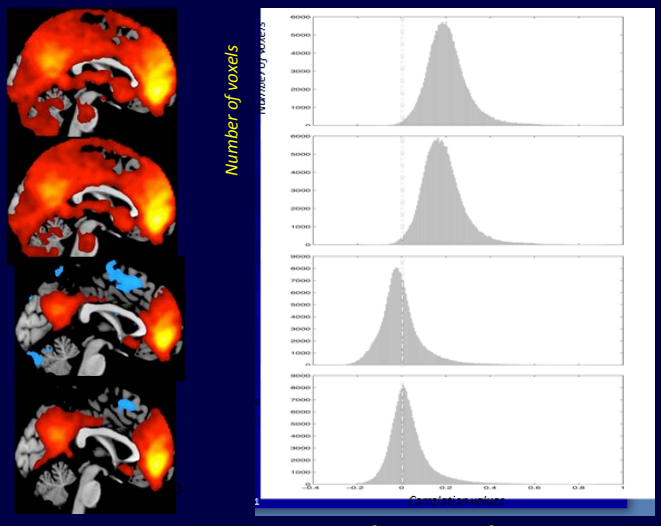
Anticorrelation: Conclusion

Bandpass filter

Movement regression

Whole brain regression

aCompCor (PCA5)



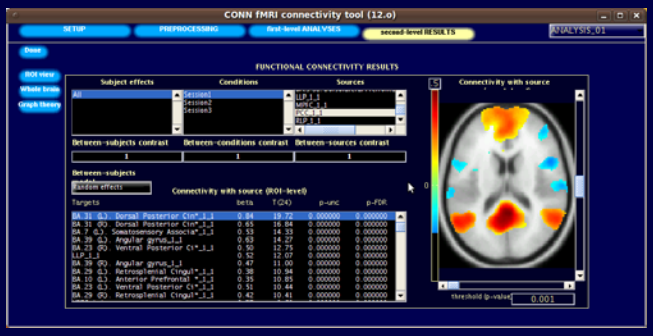
CompCor increases sensitivity/specificity and allows for the interpretation of anticorrelations

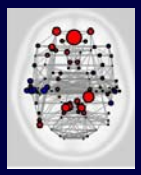
Chai et al., 2011

Conclusion

- Our results suggest that anti-correlations observed in rest-state functional connectivity are robust even without global regression and may suggest a biological origin.
- Since 2009 there has been a dramatic reduction in the number of publications on anticorrelations due to difficulty with interpretation when using gsr

CONN





Susan Whitfield-Gabrieli & Alfonso Nieto-Castanon, 2012

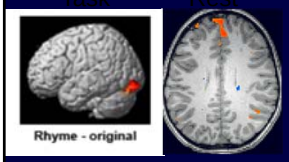
http://www.nitrc.org/projects/conn

It takes ***Art*** to do a good ***Conn*** job!

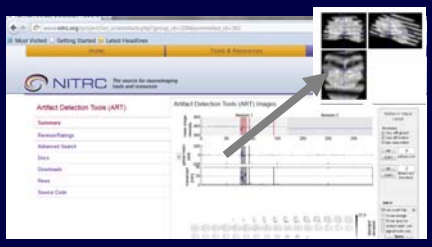
ART

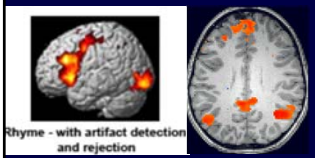
http://www.nitrc.org/projects/artifact_detect

Task Rest



Before QA





After QA

Whitfield-Gabrieli et al., in prep

The effect of motion

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

The influence of head motion on intrinsic functional connectivity MRI

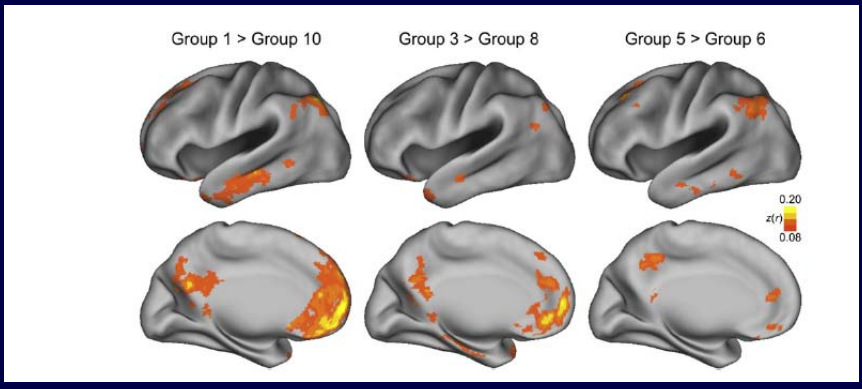
Koene R.A. Van Dijk [a,b], Mert R. Sabuncu [b,c], Randy L. Buckner [a,b,d,e,*]

N = 1000, binned according to degree of motion

Comparisons between groups of individuals with subtly different levels of head motion yielded difference maps that could be mistaken for neuronal effects . These effects are important to consider when interpreting variation between groups and across individuals.

Group comparisons based on motion (n=1000)

Group 1 (lowest 10% motion) > Group 10 (highest 10% motion)



**5 and 6 that have Mean Motion estimates of 0.044 and 0.048 mm*

Even in this small range of motion, differences in head motion yield difference map that could easily be mistaken for neuronal effects.

(Van Dijk et al., 2012)

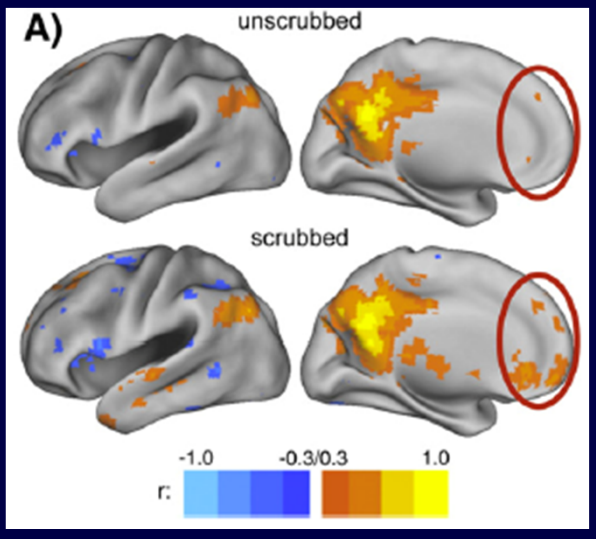
Is Regressing Motion Enough?

Artifact rejection tends to augment long-distance correlations and to decrease short-distance correlations (Power et al., 2011)

Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion

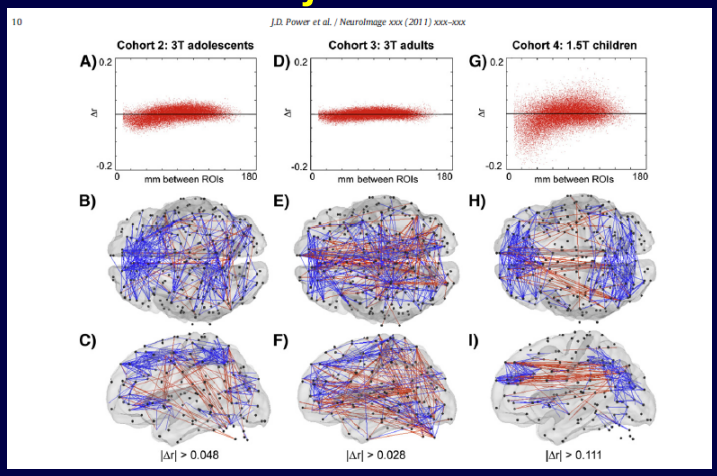
Jonathan D. Power [a,*], Kelly A. Barnes [a], Abraham Z. Snyder [a,b], Bradley L. Schlaggar [a,b,c,d], Steven E. Petersen [a,b,d,e]

Removing outliers



(Power et al., 2011)

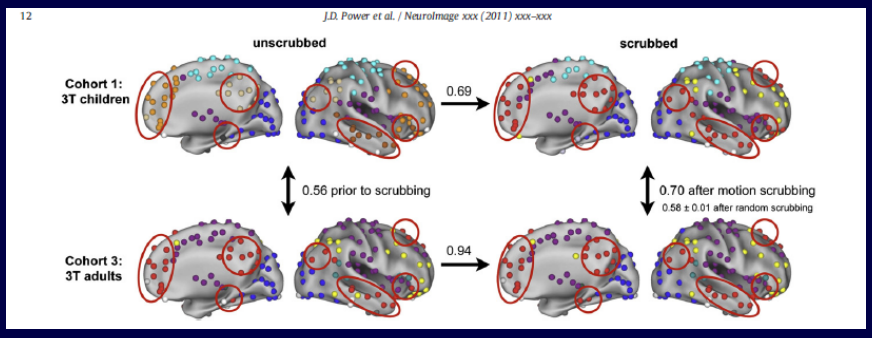
Effect of “scrubbing” artifact rejection



Increased long range (anterior/posterior) correlations & reduced local correlaions

(Power et al., 2011)

Effect of “scrubbing” or artifact rejection

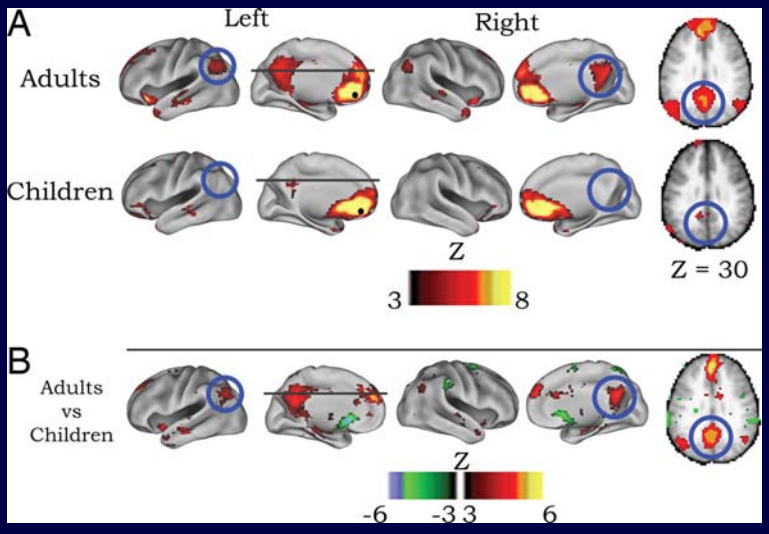


(Power et al., 2011)

Development of resting state DMN

- Within-network strength in default network increases with age (Fair et al., 2008)
- Local to distributed developmental pattern (Fair et al., 2009)

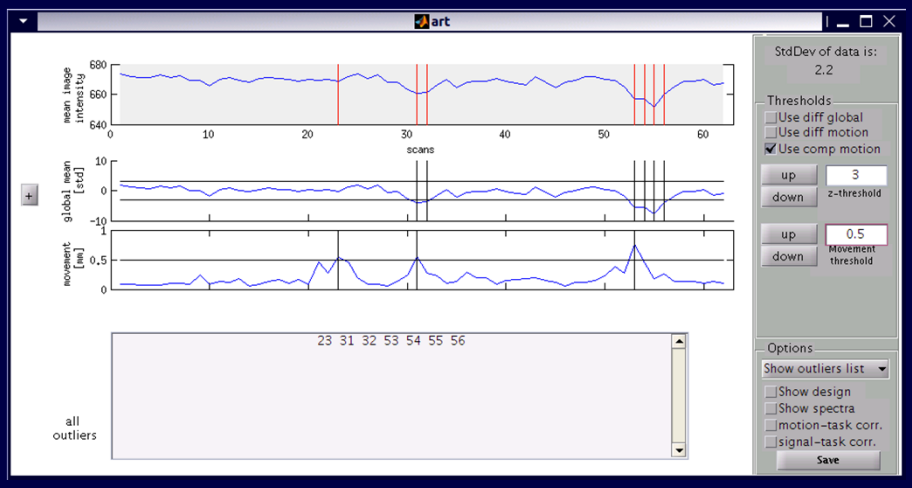
Voxelwise resting-state functional connectivity maps for a seed region (solid black circle) in mPFC



Fair D A et al. PNAS 2008;105:4028-4032

Fair et al., PNAS 2008

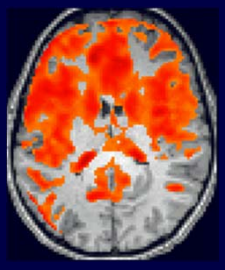
Artifact detection rs-fcMRI (Child 10yrs)



Effect of motion artifact % of BOLD variance explained

Motion parameters only

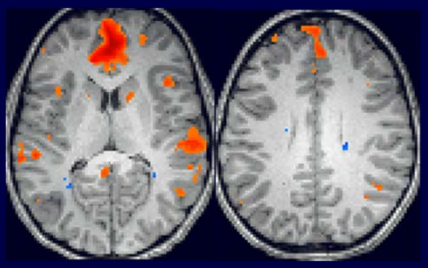
Motion parameters + outliers



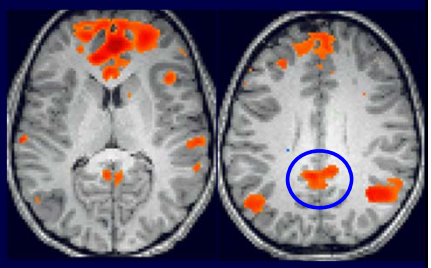
Whitfield-Gabrieli et al., In Prep

Effect of artifact rejection on first-level connectivity map (10 yr old child)

Regressing out motion parameters only

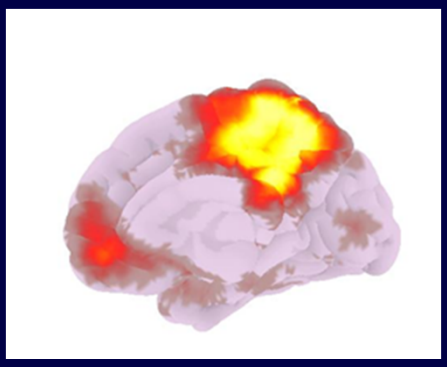


Regressing out motion parameters + outliers

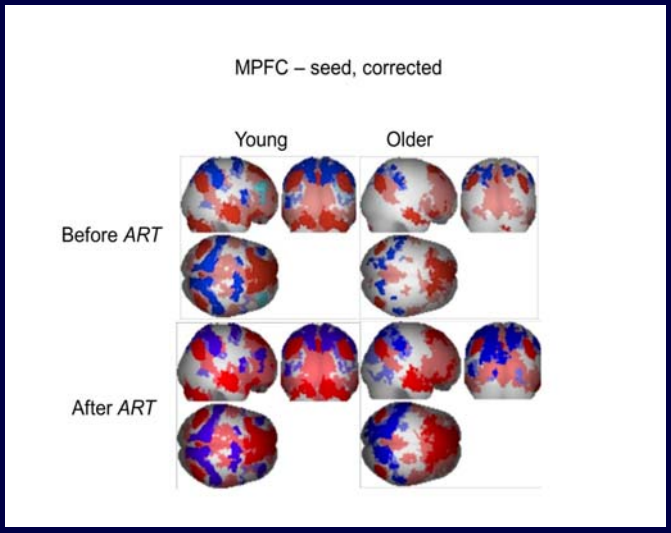


Whitfield-Gabrieli et al., In Prep

DMN even exists in Infants



Effects of regressing outliers: Young Adults and Elderly Groups



Whitfield-Gabrieli et al., In Prep

Outline

- Seed driven functional connectivity
- Resting state seed driven functional connectivity: rs-fcMRI
- Treatment of noise
- Current debates in the field (respiration/anticorrelations)
- Compcor method
- Introduction to functional conn toolbox

Functional Connectivity Overview

fMRI connectivity tool (beta)

Function: Perform functional connectivity analyses

(seeded voxel correlations)

- The toolbox implements a*CompCor* strategy for physiological (and other) noise source reduction, first-level General Linear Model for correlation and regression connectivity estimation, and second-level random-effect analyses.
- The toolbox is designed to work with both resting state scans and block designs where rest is another block amongst other conditions.

The following slides illustrate the operation of the toolbox

Steps

Step 1: Setup

Step 2: Preprocess and explore confounds

Step 3: Analyze and view 1st level results

Step 4: Define contrasts and view 2nd level results

fMRI connectivity tool (beta)

SETUP

Defines experiment information, file sources for functional data, structural data, regions of interest, and other covariates.

Setup | Preprocessing | first-level Analyses | second-level Results | Help

fMRI connectivity tool (beta)

SETUP

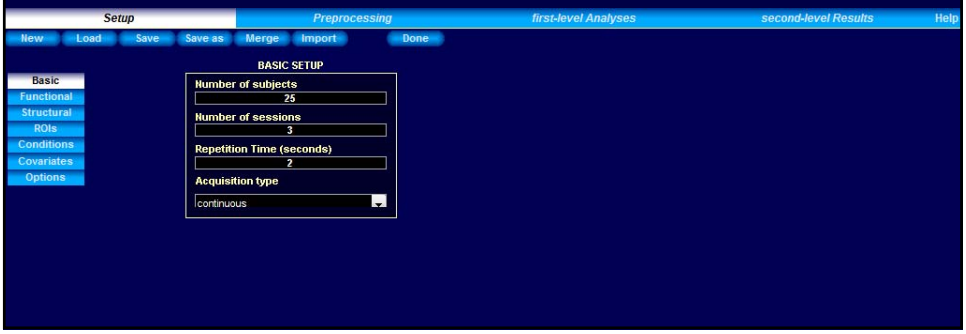
Basic : Defines basic experimental information

In this example: 25 subjects

TR = 2 seconds

3 scanning sessions per subject

The “Import” button will load predefined SPM.mat file.

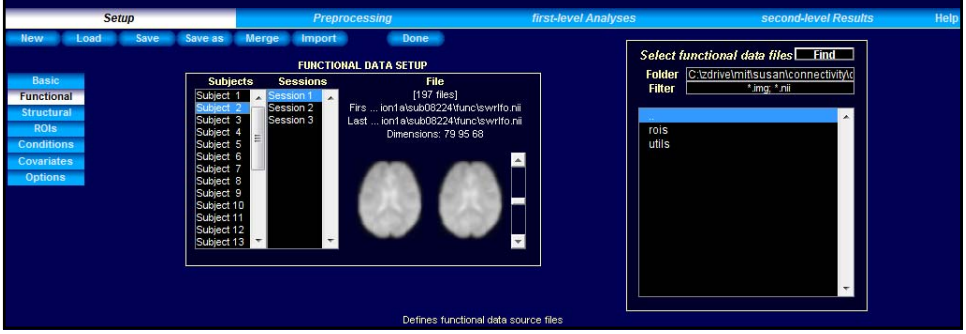


fMRI connectivity tool (beta)

SETUP

Functional : Defines functional data source files

(assumes realigned, smoothed)

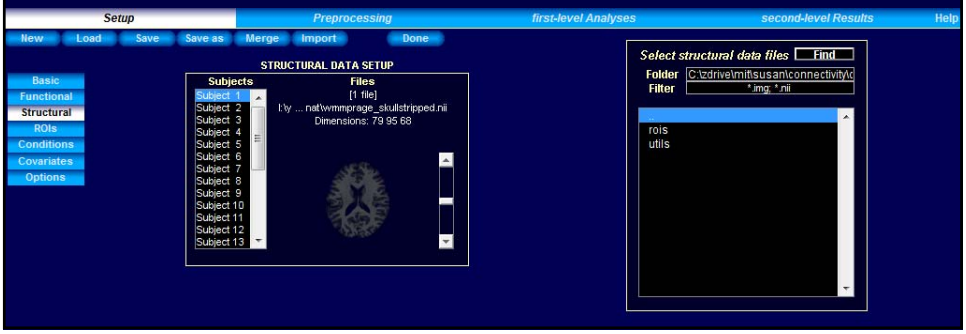


fMRI connectivity tool (beta)

SETUP

Structural : Defines structural data source files

Assumes coregistered to functional volumes –i.e. same orientation; use spm checkreg to check orientation)

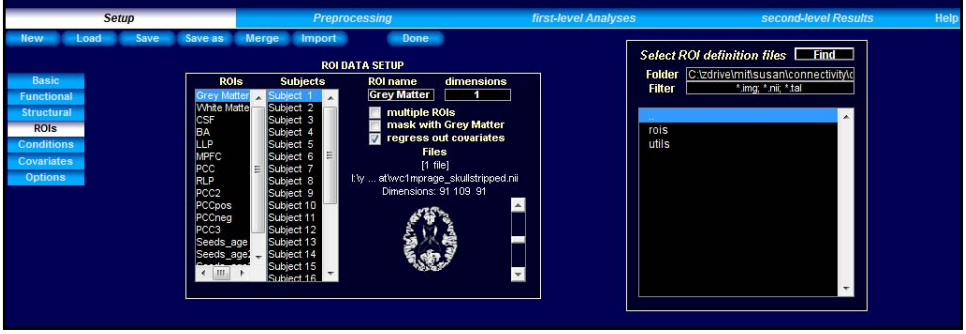


fMRI connectivity tool (beta)

SETUP

ROIs : Define ROI masks (mask files or Talairach coordinate files).

- By default all files in the *rois* toolbox folder (./conn/rois) will be imported as initial regions of interest. To import new ROIs, click below the last ROI listed.
- The special ROIs corresponding to grey matter, white matter, and CSF can be imported here (if they have already been created) or they will be automatically created from each subject structural data.
- Talairach coordinates are defined in mm

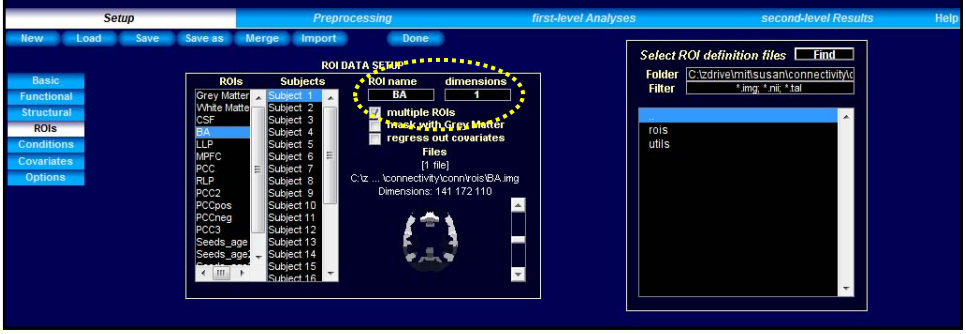


fMRI connectivity tool (beta)

SETUP

ROIs :

For each ROI a number of functional time-series (*dimensions*) can be extracted: the first time-series is the average BOLD activation within the ROI; the following time-series are the ones associated with each sequential eigenvariate (from a principal component decomposition of the BOLD activation among all voxels within the ROI).



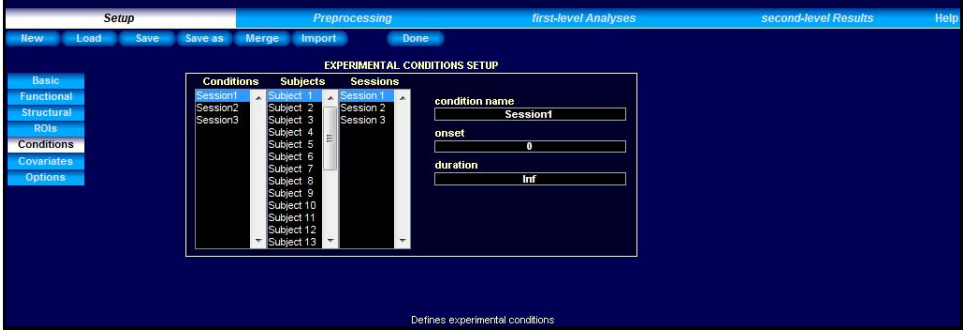
fMRI connectivity tool (beta)

SETUP

Conditions : Defines experimental conditions.

(assumes block design; conditions are defined by *onset* and *duration* of each block)

- *Onsets* and *Durations* are in seconds.

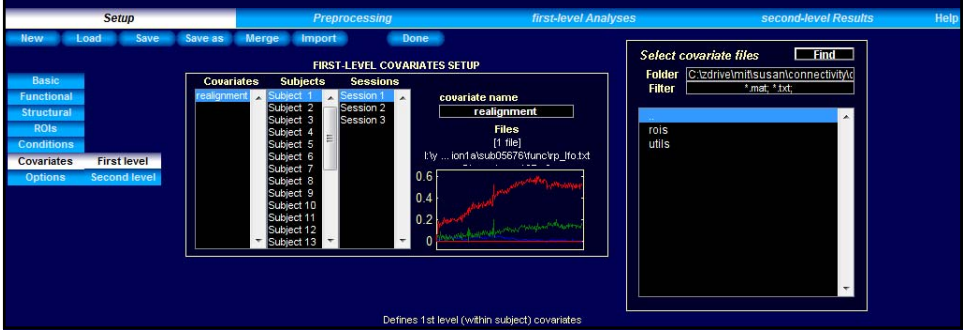


fMRI connectivity tool (beta)

SETUP

Covariates – first level: Defines within-subject covariates (e.g. realignment parameters)

(one *.txt* or *.mat* file per subject/session; files should contain as many rows as scans)

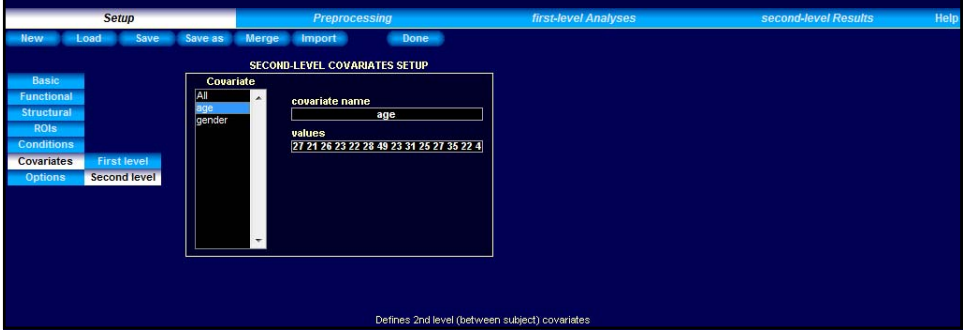


fMRI connectivity tool (beta)

SETUP

Covariates – second level: Defines between-subject covariates (e.g. subject groups)

(each covariates is defined by a vector with as many values as subjects; use 1/0 to define subject groups, or continuous values to perform between-subject regression models)

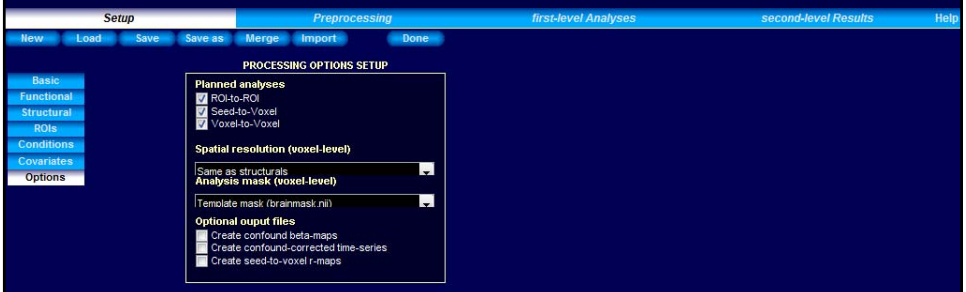


fMRI connectivity tool (beta)

SETUP

Options: Defines additional analysis options

- Planned analyses: ROI-to-ROI, Seed-to-Voxel, Voxel-to-Voxel
- Spatial resolution: voxel size for analyses (e.g. 2mm isotropic)
- Analysis mask: brainmask.nii or implicit mask (SPM subject-specific 'analysis' mask)
- Optional output files



fMRI connectivity tool (beta)

SETUP

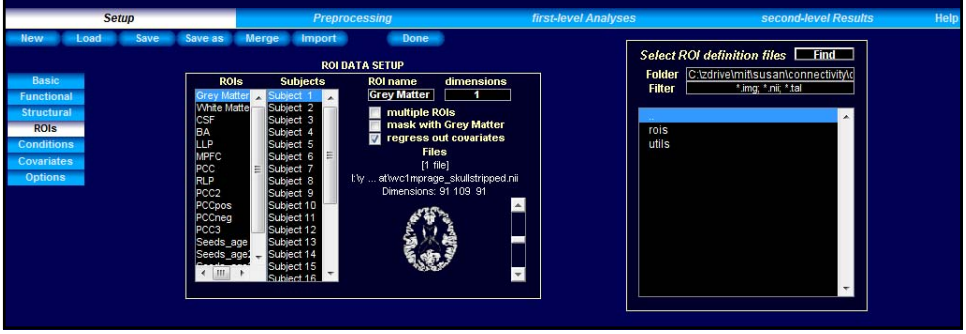
- When finished defining the experiment data press Done
  - This will import the functional data, it will also perform normalization & segmentation of the structural data in order to define gray matter/ white matter/ CSF regions of interest if these have not been already defined. Last it will extract the ROIs time-series (performing PCA on the within-ROI activations when appropriate).
  - This process could take between 5-10 minutes per subject.
  - After this process is finished come back to Setup to inspect the resulting ROIs for possible inconsistencies.
- a *conn_*.mat* file and a folder of the same name will be created for the project.
- Save / "Save as" button will save the setup configurations in a .mat file, which can be loaded later (Load button).
- The .mat file will be updated each time the "Done" button is pressed

fMRI connectivity tool (beta)

SETUP (revisited)

ROIs : If these had not been defined previously gray matter, white matter, and CSF masks will have been created now.

(check results; problems may occur when structural data is not reasonably reoriented)



Steps

Step 1: Setup

Step 2: Preprocess and explore confounds

Step 3: Analyze and view 1st level results

Step 4: Define contrasts and view 2nd level results

fMRI connectivity tool (beta)

PREPROCESSING

Define, explore, and remove possible confounds.

Any global signal that simultaneously affects otherwise unrelated areas (e.g. physiological noise, subject movement) can act as a confound in functional connectivity analyses.

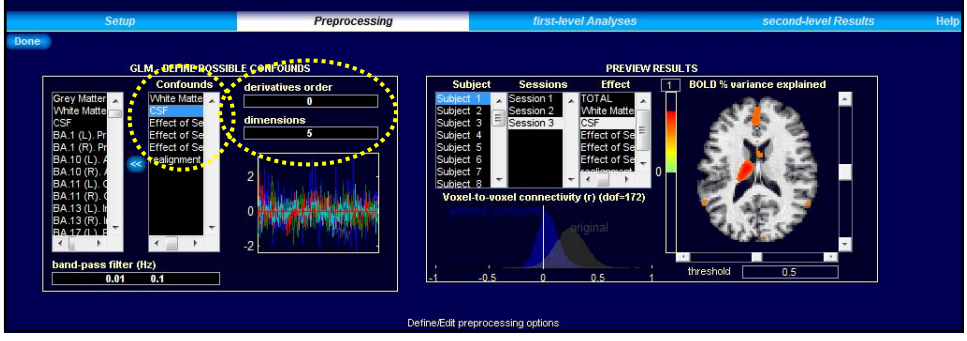
Setup | Preprocessing | first-level Analyses | second-level Results | Help

fMRI connectivity tool (beta)

PREPROCESSING

Define possible confounds:

By default the system will utilize white matter and CSF BOLD time-series (5 dimensions each), as well as any previously-defined within-subject covariate (realignment parameters) together with their first-order derivatives, and the *main* condition effects (blocks convolved with *hrf*) as possible confounds.

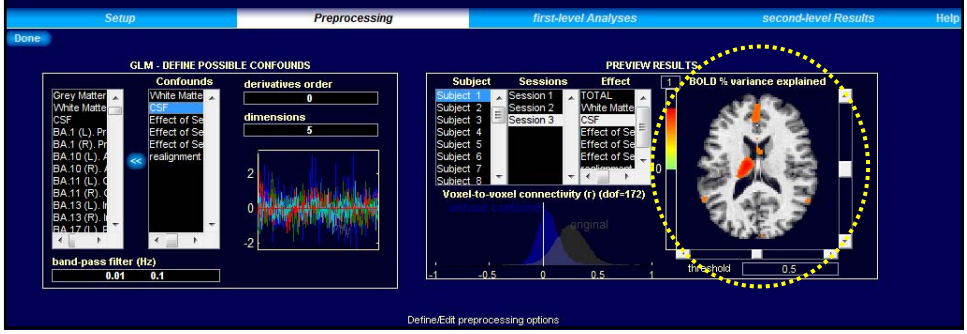


fMRI connectivity tool (beta)

PREPROCESSING

Define possible confounds:

- User can define at this step these or other possible confounds, and inspect, for each subject and session, the contribution of each confound to the BOLD response (displayed as percentage BOLD variance explained)
- Threshold in the preview window represents r-square values

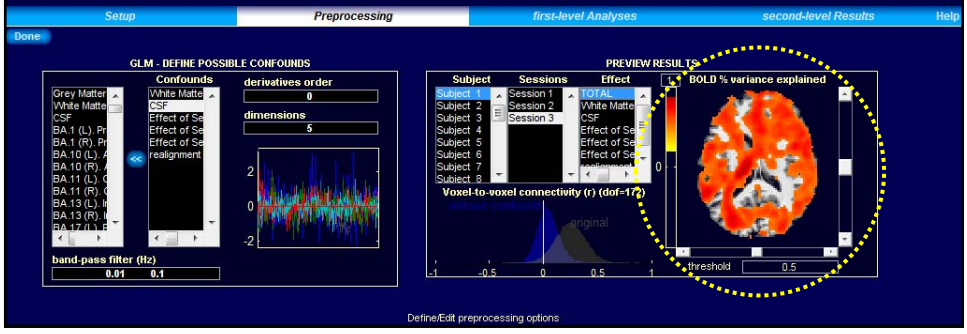


fMRI connectivity tool (beta)

PREPROCESSING

Define possible confounds:

… as well the *total* variance explained by all confounds (usually a large percentage of widespread effects, highlighting the importance of this preliminary step)

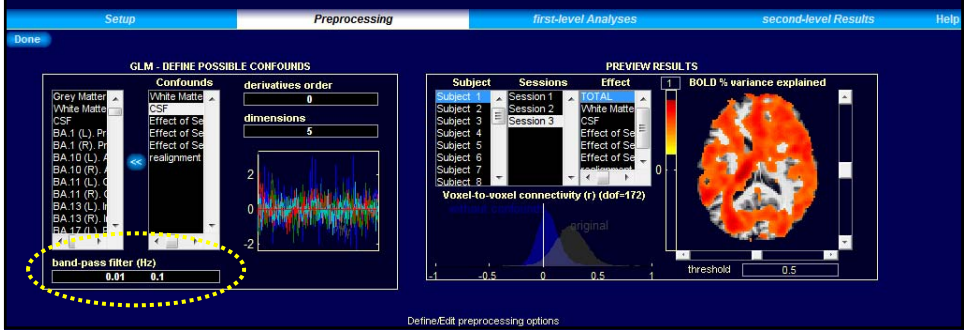


fMRI connectivity tool (beta)

PREPROCESSING

Define possible confounds:

- Last the user can also define a band-pass filter at this stage to further reduce the effect of possible confounds or to limit the subsequent connectivity analyses to a given frequency window of interest
- To see a description of an input field, point cursor to the field.



fMRI connectivity tool (beta)

PREPROCESSING

When finished defining/exploring the effect of confounds press Done. This will remove the effects of the defined confounds on all brain voxels and regions of interest.

This process could take ½ minute per subject.

After this process is finished go to the Analyses section

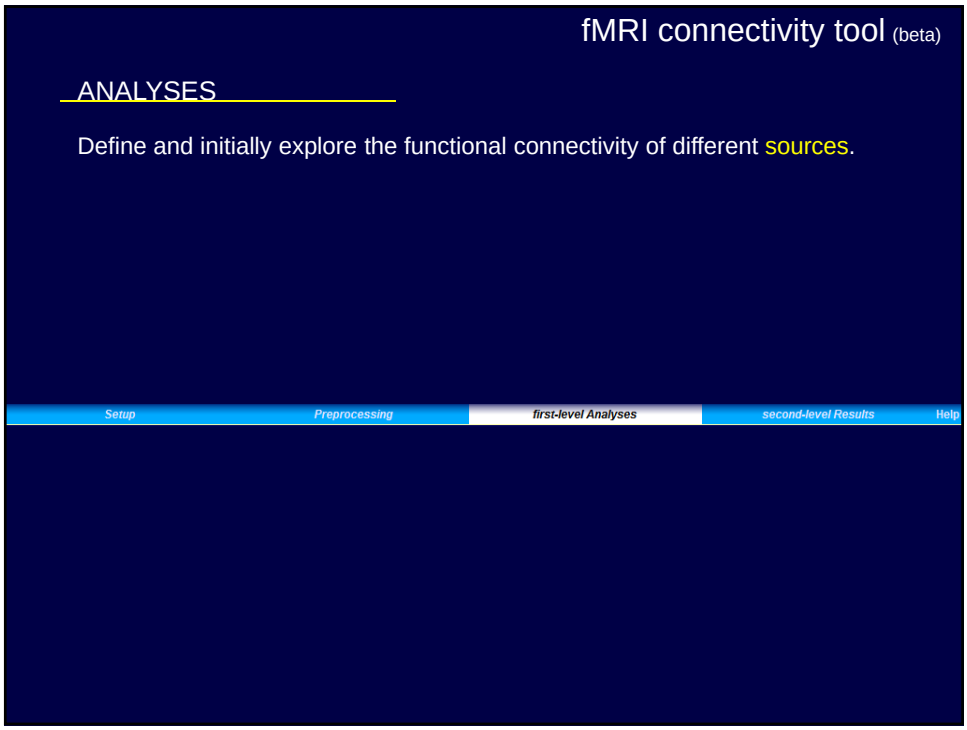
Steps

Step 1: Setup

Step 2: Preprocess and explore confounds

Step 3: Analyze and view 1st level results

Step 4: Define contrasts and view 2nd level results

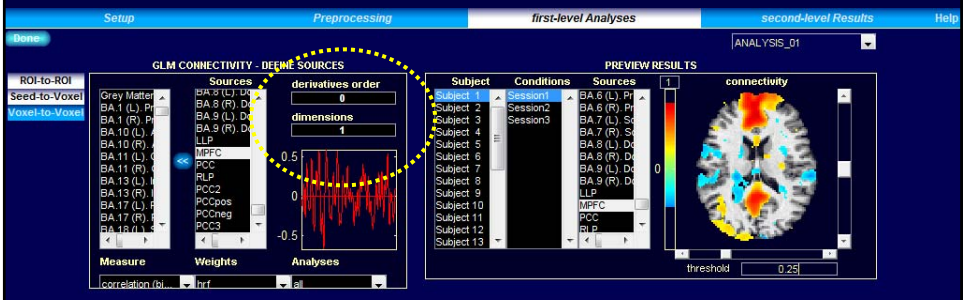


fMRI connectivity tool (beta)

ANALYSES

Define sources of interest:

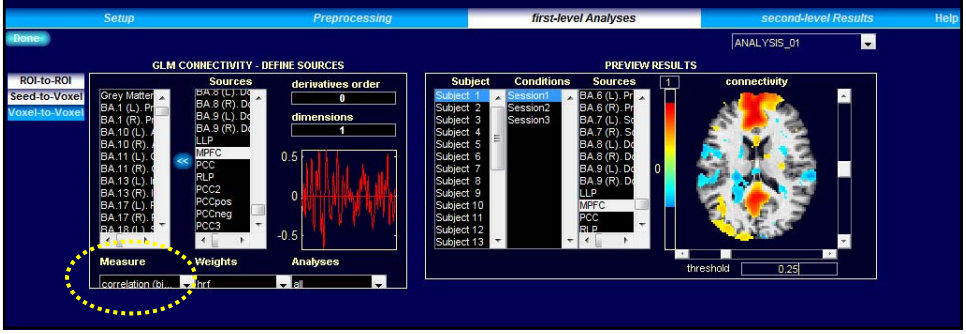
In this step the user defines the sources (ROIs) for the functional connectivity analyses. Each source can be defined by a single time-series, or it can include several time-series (several dimensions from a single ROI, or first- or higher-order derivatives of the above).



fMRI connectivity tool (beta)

ANALYSES

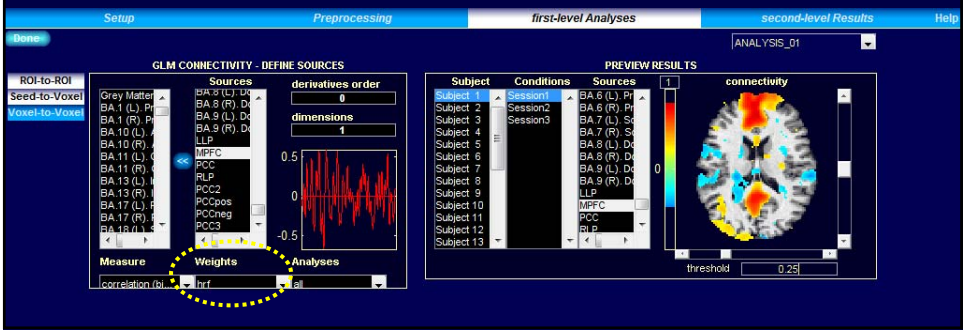
Define sources of interest: Functional connectivity analyses can be performed based on *regression* (beta values) or *correlation* (Fisher transformed) measures. In addition when multiple sources are used one can define whether the analyses should focus on *bivariate* or *semipartial* correlation measures (or *bivariate* or *multivariate* regression)



fMRI connectivity tool (beta)

ANALYSES

Within-condition weights determines how the different scans within each condition should be weighted when estimating connectivity measures. *None* weights all scans equally, *hrf* weights them with a block-convolved hrf function (incorporating expected hemodynamic delays), and *hanning* weights them using a hanning window (selecting the scans at the center of each block in order to minimize possible border effects)

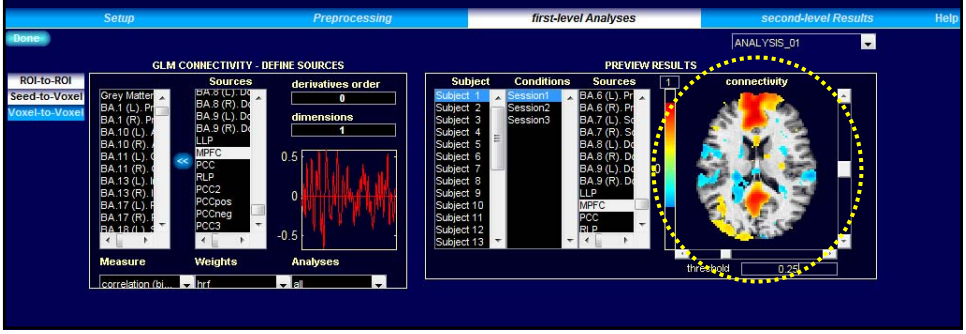


fMRI connectivity tool (beta)

ANALYSES

•At any time the resulting connectivity maps can be inspected for each subject/condition in the preview window (Analyses here are performed in real-time).

•Threshold represents correlation coefficients, or beta values for regression.



fMRI connectivity tool (beta)

ANALYSES

When finished defining/exploring the connectivity analyses press Done. This will perform the defined analyses for all subjects and allow the user to explore second-level (between subject) results.

First-level results are also exported as .nii volumes (one per Subject/Condition/Source combination) in the *results/firstlevel* folder

This process could take 1 minute per source (depending on number of subjects in the study).

Steps

Step 1: Setup

Step 2: Preprocess and explore confounds

Step 3: Analyze and view 1st level results

Step 4: Define contrasts and view 2nd level results

fMRI connectivity tool (beta)

RESULTS

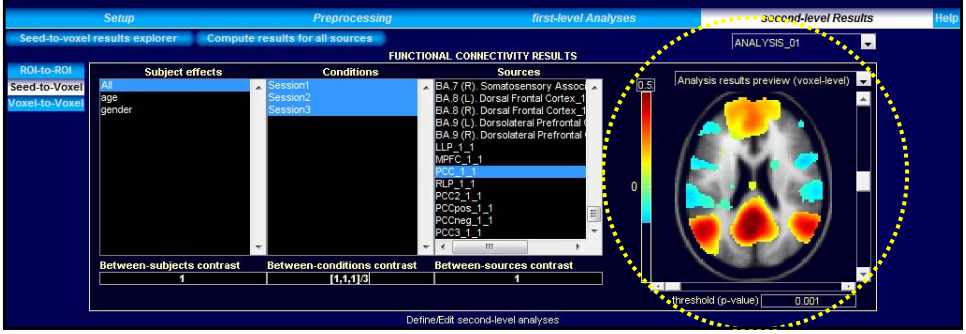
Define and explore contrasts of interest and second-level results

fMRI connectivity tool (beta)

RESULTS

Explore second-level results:

Functional connectivity measures are tested at the second-level (between-subject) using random-effect analyses. The results display shows effect sizes (measures defined in the previous step; e.g. bivariate correlation), which can be thresholded using an (uncorrected) false-positive threshold (p-values).



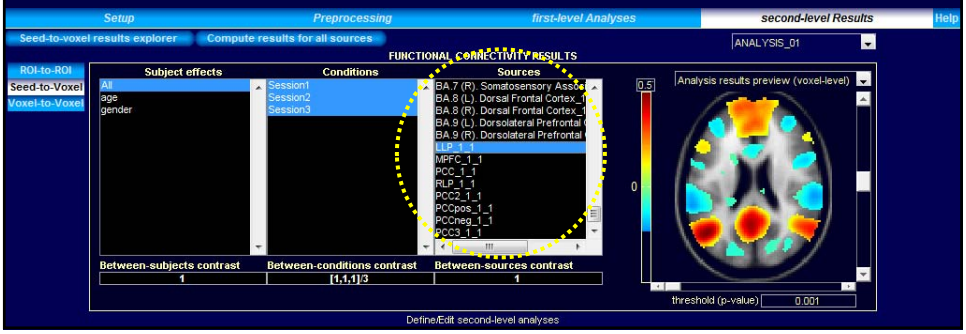
fMRI connectivity tool (beta)

RESULTS

Explore second-level results:

Each source connectivity can be tested separately simply selecting the corresponding ROI in the menu

(note: when sources were defined by multiple time-series, source names will follow the convention *ROI_DimensionNumber_DerivativeOrder*)

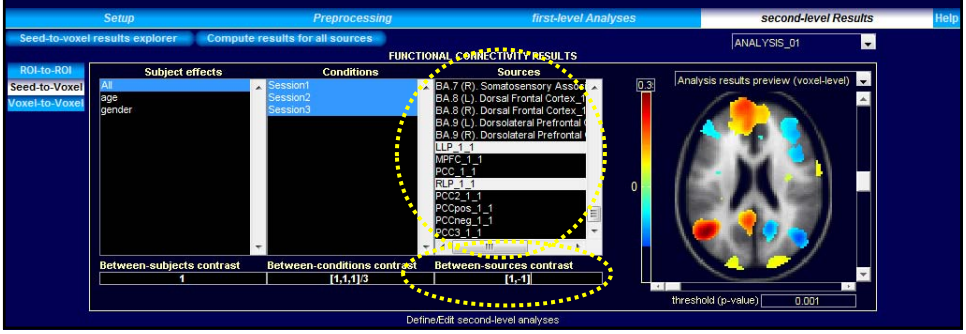


fMRI connectivity tool (beta)

RESULTS

Explore second-level results:

Multiple ROIs/sources can be selected simultaneously in order to aggregate or compare the connectivity results across several ROIs (e.g. to compare the connectivity between LLP & RLP select both sources and enter [1,-1] in the 'between-sources contrast' field)

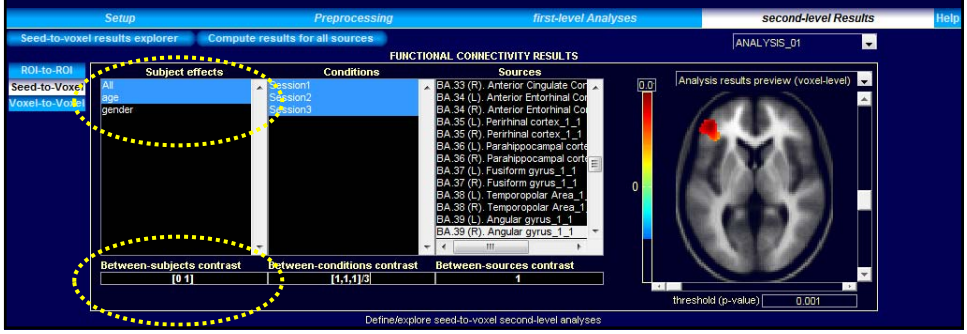


fMRI connectivity tool (beta)

RESULTS

Explore second-level results:

Selecting multiple second-level effects in the *Subject effects* list and defining *Between-subjects contrast* can be used to test more complex second-level models (e.g. regression analyses for age-related connectivity changes)

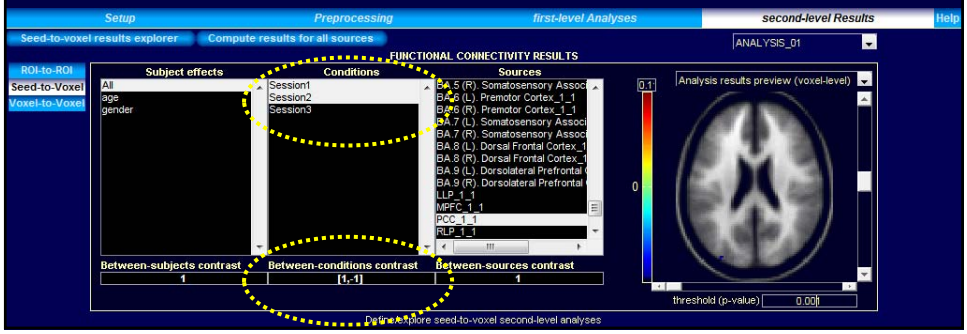


fMRI connectivity tool (beta)

RESULTS

Explore second-level results:

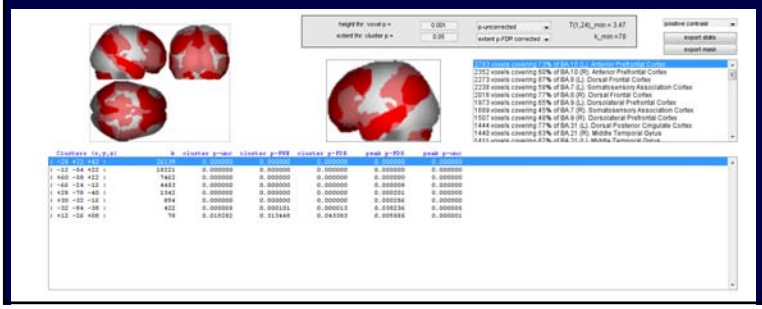
Similarly, selecting multiple conditions in the *Conditions* list and defining *Between-conditions contrast* can be used to test more complex second-level models (e.g. paired t-test for between-condition differences in connectivity)

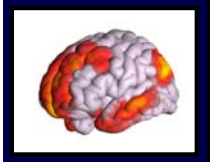


fMRI connectivity tool (beta)

Seed-to-voxel results

Selecting Seed-to-voxel results explorer exports the defined second-level model to SPM (second-level SPM.mat, beta and contrast volumes are saved in the *results/secondlevel/* folder) and it launches a new window that allows you to: explore these results using a combination of voxel-level thresholds (based on uncorrected p-values, or FDR-corrected p-values), and cluster extent thresholds (based on uncorrected cluster-level p-values, FWE- or FDR-corrected cluster-level p-values); perform one-sided or two-sided tests; export the resulting statistics; create a mask of suprathreshold voxels (e.g. for post hoc analyses); and display the results projected on the brain surface



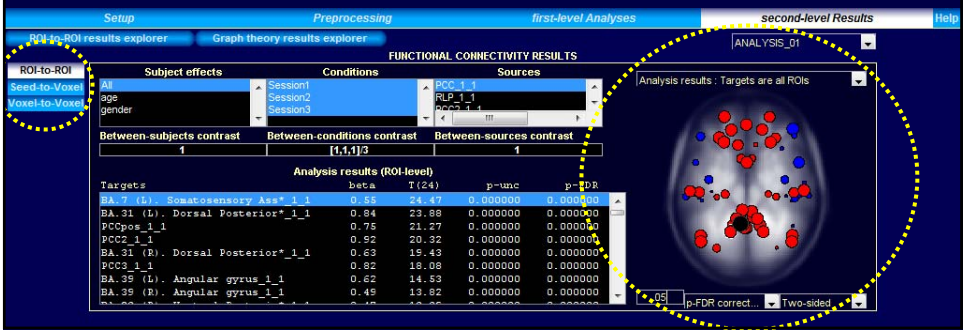


fMRI connectivity tool (beta)

ROI-to-ROI connectivity

Selecting ROI-to-ROI in the second-level results window allows you to investigate the connectivity between all of the sources/ROIs

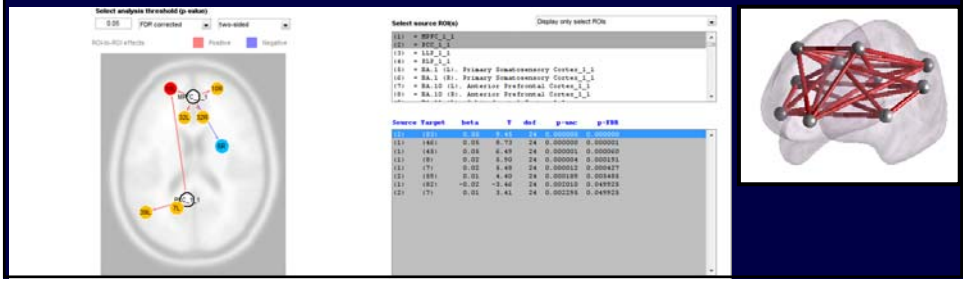
The results display shows ROI centroids (sphere sizes proportional to measures as defined in the previous step; e.g. bivariate correlation), which can be thresholded using an (uncorrected or FDR-corrected) false-positive threshold (p-values) using one- or two-sided tests.



fMRI connectivity tool (beta)

ROI-to-ROI connectivity

Selecting ROI-to-ROI results explorer launches a new window that offers additional analysis and display options for the selected second-level analysis (display the analysis results for multiple sources simultaneously, the entire ROI-to-ROI matrix or any subset of this matrix, 3d rendering display, etc.),



fMRI connectivity tool (beta)

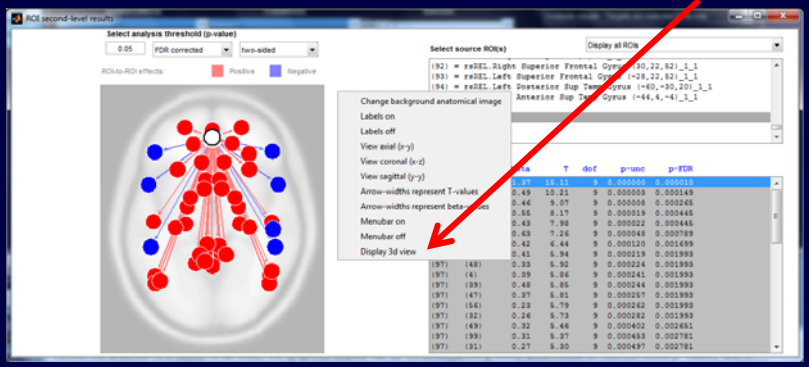
ROI-to-ROI connectivity

Example of use: ROI-level connectivity with MPFC seed

Step 2: Select *Display all ROIs (*or *Display selected ROIs only* to consider only a subset of ROIs) in the top-right menu

Select the MPFC source in the *source ROI(s)* list

Right-click on the brain display for additional options (select *3d view)*



fMRI connectivity tool (beta)

ROI-to-ROI connectivity

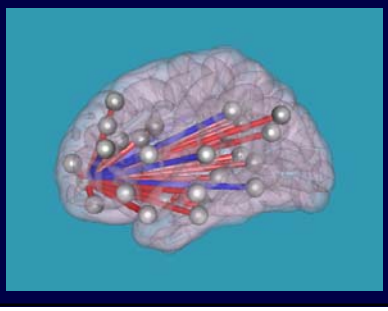
Example of use: ROI-level connectivity with MPFC seed

Step 3: Right-click on the new image again for additional display options

Select view (left/right/left-medial/right-medial/top/bottom/front/back

Select *lighting-on*

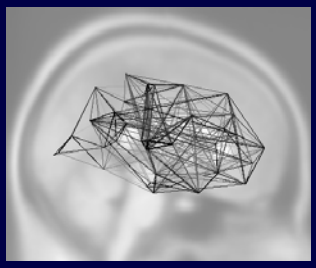
Select *menubar-on* for additional matlab figure options (rotation/zoom/print/copy/etc.)

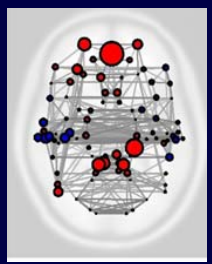


fMRI connectivity tool (beta)

Graph-theory analyses

- **ROI-to-ROI connectivity matrices provide a nice framework to investigate the functional architecture and network topology with graph theoretic analyses.**





END OVERVIEW