Clinical Applications of Functional MRI

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OUTLINE

- Brief introduction to functional MRI
- Network Models of Brain Function
  - Granger causality based directional connectivity modeling
  - Blind deconvolution of HRF
- Applications of the connectivity model
  - Autism
  - Depression
  - Schizophrenia
  - Bipolar
Biophysics of fMRI: The Vascular Network

Fig. 2.1 Cerebral Vasculature

Artery
Arterioles
Veneoles
Capillaries
Neurons

1 - 2 cm

Transit Time = 2-3 s
Measuring Brain Function using MRI
Measuring Brain Function using MRI

Brain activity

Oxygen consumption ↑
Cerebral blood flow ↑↑

Oxyhemoglobin ↑
Deoxyhemoglobin ↓

Magnetic susceptibility ↓

T2* ↑

MRI signal intensity ↑

BOLD (blood oxygenation level dependent) signal
Experimental Design

A. The Neural Activation

B. The BOLD Signal

C. The BOLD signal responding to a single neural activation.

Block Design

Event-related Design
Echo-planar Imaging
Donder’s Method: Subtraction

Example: How long does it take to choose between alternatives? (Mental Chronometry)

- A random series of A’s and B’s presented and the subject must:
  - Task 1 - Respond whenever event A or B occurs (RT₁)
  - Task 2 - Respond only to A not to B (RT₂)
  - Task 3 - Respond X to A and Y to B (RT₃)

RT = reaction time

- RT₁ = T-detect + T-response
- RT₂ = T-detect + T-discrimination + T-response
- RT₃ = T-detect + T-discrimination + T-choice + T-response
- T-discrimination = RT₂ - RT₁
- T-choice = RT₃ - RT₂
Criticisms of Donder

- Assumes that adding components does not affect other components (i.e. assumption of pure insertion)
- One should pick tasks that differ along same dimension (time in our example)
General Linear Model (GLM)

Parcel out variance in the voxel’s time course to the contributions of two predictors plus residual noise (what the predictors can’t account for).

\[
\beta_1 \times \text{Faces} + \beta_2 \times \text{Places} + \text{residuals}
\]
GLM Stats

<table>
<thead>
<tr>
<th>Predictor</th>
<th>beta</th>
<th>se</th>
<th>t</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>faces left</td>
<td>1.793</td>
<td>0.132</td>
<td>13.539</td>
<td>0.000000</td>
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<tr>
<td>faces right</td>
<td>0.987</td>
<td>0.132</td>
<td>7.451</td>
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<td>1.848</td>
<td>0.132</td>
<td>13.956</td>
<td>0.000000</td>
</tr>
<tr>
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<td>0.672</td>
<td>0.132</td>
<td>5.075</td>
<td>0.000001</td>
</tr>
<tr>
<td>places right</td>
<td>0.429</td>
<td>0.132</td>
<td>3.237</td>
<td>0.001273</td>
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<tr>
<td>places fovea</td>
<td>0.631</td>
<td>0.132</td>
<td>4.769</td>
<td>0.000002</td>
</tr>
</tbody>
</table>

blue: original time course
green: best fitting model
red: residuals
Data pre-processing techniques

Head Motion Correction

- Rigid body transformation
  - 6 parameters: 3 translation, 3 rotation
- Minimization of some cost function
  - E.g., sum of squared differences
  - Mutual information
Co-Registration and Normalization

Matching two images of the same subject’s brain collected using different pulse sequences.

Matching an image from a single subject, typically a high-resolution anatomical, to a template in a standardized space.

Structural

Functional

Coregistered

Original image
Spatially normalised

MNI template = average brain of >200 subjects (high resolution T1)

Spatial Normalisation
Template image
**NETWORK MODELS OF BRAIN FUNCTION**

**Functional Localization**
Assumes temporal evolution of function to be spatially independent

**Functional Networks**
Assumes temporal evolution of function to be spatially dependent (distributed information processing)
APPROACHES

- Functional connectivity
  - Correlation Coefficient

- Effective connectivity
  - Dynamic Causal Modelling
  - Structural Equation Modeling
  - Granger Causality
Granger causality is based on the concept of **temporal precedence** information.

If including past values of $Y$ improves the prediction of future values of $X$, then $Y$ is said to have a causal influence on $X$.

Originally invented by Granger for stock market prediction and awarded Nobel prize in economics in 2003.
Why Causality?

- Movie of dynamic brain function showing causal sequence of activation during a tactile spatial discrimination task using EEG source localization
CORRELATION PURGED GRANGER CAUSALITY [CPGC]

Given $k$ time series $X(t) = [x_1(t) \ x_2(t) \ \ldots \ x_k(t)]$, (order of model $p$)

$$X(t) = \sum_{n=1}^{p} A(n)X(t-n) + E(t)$$

$A(1) \ \ldots \ A(p)$ : coefficients of the model

$E(t)$ : model error

In order to account for the zero-lag correlation effects, we introduce the zero-lag term

$$X(t) = \sum_{n=0}^{p} A'(n)X(t-n) + E'(t)$$

GC obtained from $A'(1) \ \ldots \ A'(p)$ are linearly independent of zero-lag correlation, which we call correlation-purged GC (CPGC).

$$CPGC_{ij} = \sum_{n=1}^{p} [a_{ij}'(n)]^2$$
The dynamic model has time varying model parameters $A(n,t)$ of order $p$ and model error $E(t)$ is given by

$$X(t) = \sum_{n=0}^{p} A'(n,t) X(t-n) + E'(t)$$

Here $A'(n,t)$ represents the model parameters with the zero-lag term included.

Dynamic Granger causality (DGC) can then be obtained as shown below

$$DGC_{ij}(t) = \sum_{n=1}^{p} a'_{ij}[n, t]$$
Concerns

- Variability of hemodynamic response across regions and subjects, part of which is shown to be structural and non-neuronal in origin.

- Using raw fMRI data in Granger causality analysis could confound causality values.

Solution

- Deconvolving out the HRF from the fMRI signal to obtain the latent neuronal response.

- Using these hidden neuronal variables in connectivity analysis instead of raw fMRI time series.
Data Acquisition
- fMRI data is acquired from the scanner.
- Acquired data is preprocessed and time series are extracted from activated ROIs

Deconvolution
- Extracted time series are deconvolved
- Neuronal response is obtained

Connectivity Analysis
- Connectivity Matrix is obtained
- Statistical tests are then performed to obtain significant paths
Blind deconvolution

- To find the hidden neuronal variable by deconvolving the measured fMRI signal without any knowledge of the HRF transfer function.
'Kalman Filters

<table>
<thead>
<tr>
<th>Observed</th>
<th>Time = k-1</th>
<th>Time = k</th>
<th>Time = k+1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplied by user</td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
</tbody>
</table>

Hidden

\[
x_k = F_k x_{k-1} + B_k u_k + w_k
\]

\[
w_k \sim N(0, Q_{wk})
\]

\[
z_k = H_k x_k + v_k
\]

\[
v_k \sim N(0, R_{vk})
\]

**Time Update ("Predict")**

1. Project the state ahead
   \[
   \hat{x}_k = A\hat{x}_{k-1} + B u_{k-1}
   \]
2. Project the error covariance ahead
   \[
   P_k = A P_{k-1} A^T + Q
   \]

**Measurement Update ("Correct")**

1. Compute the Kalman gain
   \[
   K_k = P_k H^T (H P_k H^T + R)^{-1}
   \]
2. Update estimate with measurement \(z_k\)
   \[
   \hat{x}_k = \hat{x}_k + K_k (z_k - H \hat{x}_k)
   \]
3. Update the error covariance
   \[
   P_k = (I - K_k H) P_k
   \]
CPGC connectivity analysis

DGC connectivity analysis.
APPLICATIONS
Why?

- Psychiatric or mental disorders are subjectively diagnosed based on behavior.

- Treatments using drugs are not targeted, rather they affect neurotransmitters which are widely available in the brain.

- So, we need MECHANISTIC models of mental disorders.
Identification of neural connectivity signatures of autism using machine learning

- **Autism**: Is a highly varying neural development disorder.

- **Recent neurobiological theories**: Suggest interregional connection abnormalities as a hallmark of the pathobiology of autism.

- **Earlier Findings**: Altered functional and anatomical connectivity have been reported widely in complex cognitive and social tasks in autism.

- **The current fMRI study**: Focuses on the possibility of using effective connectivity measures as a potential biomarker for diagnosis of autism.

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Identification of neural connectivity signatures of autism using machine learning

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³ Department of Psychology, University of Alabama at Birmingham, Birmingham, AL, USA
DATA ACQUISITION

- fMRI data were acquired on a Siemens 3T Allegra scanner with a TR of 1000ms.

15 Autistic Subjects

15 Control Subjects

MRI SCANNER

Series of comic strip vignettes

Experimental condition A
- Intentional causality
  Participants relied on social rules or ToM (Theory of Mind) to arrive at their judgment.

Experimental condition B
- Physical causality
  Participants relied on laws of physics to arrive at their judgment.
Brain State Classification

Supervised Learning

Input:
\[ X_1 \quad X_2 \quad X_3 \]

Output:
\[ y_1 \quad y_2 \quad y_3 \]

Learning Methodology

Automatic procedures that learn a task from a series of examples

Training Examples:
\[ (X_1, y_1), (X_2, y_2), \ldots, (X_n, y_n) \]

Learning/Training
Generate a function \( f \) using support vector machine (SVM) such that
\[ f(X_i) \rightarrow y_i \]

Test Example
\[ X_i \]

Test
Prediction
\[ f(X_i) = y_i \]
Classical approach: Mass Univariate Analysis

**Input**
- BOLD
- Time
- 1. Voxel time series
- 2. Experimental Design

**Output**
- e.g. GLM
- Map: Activated regions
- task 1 vs. task 2

Pattern recognition approach: Multivariate Analysis

**Input**
- SVM - training
- Time points from task 1
- Time points from task 2
- New example

**Output**
- SVM - test
- Map: Discriminating regions between task 1 and task 2
- Prediction: task 1 or task 2
Classification with individual volumes

Could we use connectivity path weights instead of BOLD intensities for SVM?
RCE-SVM

1. Metrics of 15 controls and 15 autistic subjects
2. Training data from 8 control and 8 autistic subjects
3. Cluster the input metrics into n clusters using k-means
4. Calculate the score of each cluster using the average accuracy of prediction by SVM using 10 folds
5. Remove the clusters with scores in the bottom 10%. Set n=1-0.1n
6. Repeat 50 times
7. Testing data from 7 control and 7 autistic subjects
8. Evaluate classification accuracy on test data each of the 50 times.
9. Merge the clusters
   - Is n=2?
     - Yes: Stop
     - No: Continue
RESULTS & CONCLUSION

Graph showing classification accuracy, sensitivity and specificity obtained by simultaneously using the following features: behavioral scores, functional connectivity, effective connectivity and fractional anisotropy obtained from DTI. The X-axis shows number of clusters/number of features and the Y-axis, the performance (classification accuracy, sensitivity and specificity).
RESULTS & CONCLUSION

Mean of nineteen paths which was most important for giving maximum classification accuracy for autism and control groups. All paths had significantly decreased connectivity ($p<0.05$ corrected using Bonferroni method for 18 paths; for one of the paths $p<0.05$ uncorrected) in the Autism group as compared to controls. The bars represent standard errors.
The nineteen paths whose effective connectivity values were top-ranked features for classification of the two groups (Autism and Controls) with the maximum accuracy (Left panel: participants with autism; and right panel: control participants). The width of the arrows represents the path strength and the color of the path indicates its rank obtained during classification with 1 being the most significant and 19 being the least significant.
### Results & Conclusion

<table>
<thead>
<tr>
<th>Source Region → Sink Region</th>
<th>p-value</th>
<th>Correlation Coefficient</th>
<th>Source Region → Sink Region</th>
<th>p-value</th>
<th>Correlation Coefficient</th>
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<tr>
<td>LMTG → LTPJ</td>
<td>0.0003</td>
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<td>RFFG → RSPL</td>
<td>0.0425</td>
<td>0.3727</td>
</tr>
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</table>
Distinct phenotypes associated with pathophysiology of major depressive disorder (MDD)

- A hyper-responsive subtype among trauma-exposed MDD.
- A hypo-responsive subtype among never trauma-exposed MDD.

Earlier findings: Demonstrated key roles for medial and lateral prefrontal cortex (PFC) in modulation of limbic response to stress.

The Current fMRI study: Investigates whether differential amygdala reactivity within MDD based on early life stress history was associated with failure of inhibition from medial or lateral PFC.
Participants performed a gender identification variant of the Eriksen flanker task[5].

The task was designed to identify the influence of valence on the efficiency of selective attention by emotion (positive, negative, and neutral).
METHOD

Effective connectivity schematic
RESULTS & CONCLUSION

MDD > Controls

Controls > MDD

MDD > Controls
Correlation between path BA32L→dIPFCR, and physical neglect.

Correlation between path BA32L→Right Amygdala, and physical neglect.
Effective connectivity analysis of the memory network in schizophrenia before and after antipsychotic medication

- **Schizophrenia**: A severe and disabling mental disorder

- **Previous work**: Has shown that patients with schizophrenia (SZ) have memory disruptions, which often do not improve with antipsychotic medication.

- **The current study**: Investigated if participants with SZ showed significant alterations within the memory network compared to healthy controls and whether these connections improved with medication
DATA ACQUISITION

Baseline

Week 1

21 SZ Off medication
20 Healthy Controls

Deep Encoding Phase

Alive?

Pheasant

*

Alive?

Turbine

Retrieval Phase

Ready?

Turbine

*

Ready?

Satchel
**RESULTS & CONCLUSION**

Paths that were (left) significantly greater in healthy control than unmedicated schizophrenia (HC > SZ) (right) paths that were significantly greater in unmedicated schizophrenia compared to healthy controls (SZ > HC)

Paths that were (left) significantly greater in patients with schizophrenia after medication (Medicated SZ > Unmedicated SZ) and (right) paths that were significantly greater before medication (Unmedicated SZ > Medicated).
Effectiveness Connectivity Among Three Large-Scale Networks in Schizophrenia and Bipolar Disorder with Psychosis

- **Schizophrenia & Bipolar Disorder**: Severe and disabling mental disorders.

- These disorders display more shared than unique abnormalities.

- However, the clinical course and functional outcome of these disorders are notably divergent.

- **The current study**: We compared the EC using a triple network model in patients with schizophrenia and psychotic bipolar disorder to establish the diagnostic classification accuracy that can be achieved using this model.
DATA ACQUISITION

38 medicated, clinically stable patients with DSM-IV Schizophrenia Disorder

19 subjects with psychotic bipolar disorder

10 minutes resting fMRI

- Preprocessing included SPM-8 based slice-timing correction, rigid body registration and realignment.
- Retrospective physiological correction was performed (Retroicor).
- ArtRepair was used to correct movement artifacts.
- Spatial smoothing was done using 8mm FWHM kernel.
- Variance accounted for by nuisance covariates (6 head motion parameters, global mean signal, white-matter signal and CSF signal) was removed by regression.
METHOD

Acquire Data

Effective Connectivity Model

Causal connectivity weights -> RCE-SVM classifier1
Behavioral Scores -> RCE-SVM classifier2
Combined -> RCE-SVM classifier3
(left) Paths significantly stronger in bipolar participants compared to schizophrenia participants. (right) Paths significantly stronger in schizophrenia participants compared to bipolar participants.
RESULTS & CONCLUSION

- **EC classifier**
  - Accuracy 82.5%
  - 19 feature clusters
  - 37 EC paths

- **Behavioral Classifier**
  - Accuracy 66.7%
  - 2 feature clusters
  - 3 Behaviors

- **Combined Classifier**
  - Accuracy 90.9%
  - 4 feature clusters
  - 10 features
Dynamics of functional and effective brain connectivity better predicts disease state compared to traditional static connectivity

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Motivation, hypothesis and major work

- **Motivation**: Is dynamics of connectivity a better predictor of PTSD than static connectivity

- **Hypothesis**: dynamics of connectivity may be more sensitive to the change brought by mental disorders than conventional connectivity

- **Major work**: A unified framework involving
  - Dynamic and static estimation of whole brain EC and FC
  - Adaptive windowing
  - Classify PTSD and healthy controls using recursive clustering elimination based support vector machine (RCE-SVM)
Materials and Methods

Data acquisition & Preprocessing

- PTSD patients and healthy controls were recruited after the 2008 Wenchuan earthquake, Sichuan, China. 99 runs from 76 healthy people and 146 runs from 73 PTSD patients
- T2*-weighted echo planar imaging functional images: 200 volumes per scan, In-plane matrix of 64×64 (voxels), 30 axial slices, field of view (FOV) =220×220mm², FA=90˚, TR/TE=2000ms/30ms, slice thickness 4mm with 1 mm gap.

Data Processing Assistant for Resting-State fMRI (DPARSF)

- Slice timing
- Realignment
- Normalization
- Smoothing
- Bandpass filtering 0.01-0.1Hz
- WM& CSF signal regression out
- Detrending
- Mean time series extraction from 190 regions

Mean time series extraction from 190 regions
Procedures of the methodology to distinguish PTSD and controls

- fMRI data
  - Preprocessing
    - Connectivity calculation
      - Dynamic Granger causality for DEC
        - T-test filtering
          - RCE-SVM classification
            - Significant features (connectivities) PTSD>Controls & PTSD<Controls
      - Correlation purged Granger causality for SEC
        - T-test filtering
          - RCE-SVM classification
            - Significant features (connectivities) PTSD>Controls & PTSD<Controls
      - Dynamic instantaneous correlation for DFC
        - T-test filtering
          - RCE-SVM classification
            - Significant features (connectivities) PTSD>Controls & PTSD<Controls
      - Static instantaneous correlation for SFC
        - T-test filtering
          - RCE-SVM classification
            - Significant features (connectivities) PTSD>Controls & PTSD<Controls

Classification performance comparison
Dynamic & static FC estimation

Dynamic FC

- Sliding window

Static FC

- Overall Pearson's correlation between two time series

- The minimum window length when all 190 time series pass DF test is selected

- Dickey-Fuller test for stationarity
Dynamic & static EC estimation

\[ X(t) = V(t) + \sum_{n=1}^{p} A(n, t)X(t - n) + E(t) \]

Dynamic EC

\[ DG_{ij}(t) = \sum_{n=1}^{p} a_{ij}^2(n, t) \]

Static EC

\[ X(t) = V + \sum_{n=1}^{p} A(n)X(t - n) + E(t) \]

\[ D_{ij} = \sum_{n=1}^{p} a_{ij}^2(n) \]

Correlation purged Granger causality (CPGC)

\[ X(t) = V + \sum_{n=0}^{p} A'(n)X(t - n) + E'(t) \]

\[ CPG_{ij} = \sum_{n=1}^{p} [a'_{ij}(n)]^2 \]

\[ FF = \arg\{\min\{\text{var}(\hat{E}(t))^2\}\} \]

Bayesian information criterion for order

Error variance minimization criterion for forgetting factor
Dynamic Granger causality

Subject 1  Subject 2  Subject n

Initial condition

Updating Kalman coefficients

Kalman state variables representing group values

Dynamic Granger causality
Flowchart of RCE-SVM algorithm for scenario in this work

Connectivity data of 146 PTSD and 99 healthy controls are grouped into 10 subsets by subjects

For each subset RCE-SVM is effected, and results for cross validation

Data of half of subjects is for training

Data of half of subjects is for testing

Cluster features into n clusters using k-means, n=40

Calculate score of every cluster according to its SVM classification accuracy using randomized 6 folds

Re-randomize data into 6 folds

Re-cluster the remaining features using k-means

Evaluate the classification accuracy on testing data

Repetition number = 100?

Yes

Eliminate 50% clusters with low scores

Only one cluster left?

Yes

End
Results

Connectivity dynamics is more discriminative of PTSD than static connectivity

Dynamic connectivity is shown as green

Static connectivity is shown as blue

Number of clusters / number of paths
Brain networks revealed by comparing PTSD and healthy controls using connectivity metrics. (p=0.05)
Brain networks revealed by comparing PTSD and healthy controls using connectivity metrics. (p=0.05)
Variance of DFC: Control > PTSD
SFC: PTSD > Control

Note: there is no significant path for healthy controls < PTSD in terms of variance of DFC and healthy controls > PTSD in terms of SFC
Discussion

- Decreased temporal variability of connectivity and thus less flexible switching between different brain states are signature of PTSD.

- In terms of variance of DFC and DEC, many significant paths for which healthy controls > PTSD while very few paths of PTSD > control.

- In terms of SEC and SFC, few paths of healthy controls > PTSD and quite a lot of significant paths of PTSD > control.

- The RCE-SVM classifier using dynamics of connectivity as features outperformed that with static measures of connectivity.
Application to Indian Systems of Medicine: Investigation into OM

- Vagal nerve stimulation is an invasive technique used to induce limbic deactivation in psychiatric disorders

- Hypothesis: OM sound is a non-invasive technique that can be used to induce limbic deactivation
Methods


<table>
<thead>
<tr>
<th>15 Seconds</th>
<th>'OM'</th>
<th>15 Seconds</th>
<th>SSSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>REST</td>
<td>15 Seconds</td>
<td>REST</td>
<td>15 Seconds</td>
</tr>
</tbody>
</table>

Compare conditions using t-test

\[ \text{DGC}_{ij} \]
Results: OM < REST
Results: OM < SSS
Sneak peak into basic science applications
Acknowledgements

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