COGNITIVE ABILITIES AND BRAIN CONNECTIVITY
-A Resting State fMRI Study

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A thesis submitted towards partial fulfillment of

BS-MS Dual Degree Programme

by

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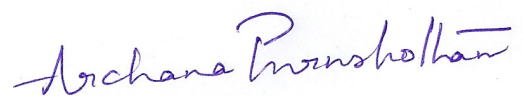

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CERTIFICATE

This is to certify that this dissertation entitled "Cognitive Abilities And Brain Connectivity" submitted towards the partial fulfillment of the BS-MS dual degree programme at the Indian Institute of Science Education and Research, Pune represents original research carried out by "Poortata Shirish Lalwani" at the "CBDR, inStem, NCBS, Bangalore" under the supervision of "Dr. Archana Purushotham" during the academic year 2014-2015.
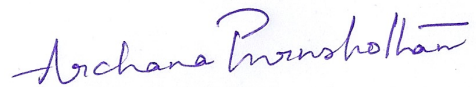
Student

Poortata Lalwani

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DECLARATION

I hereby declare that the matter embodied in the report entitled "Cognitive Abilities And Brain Connectivity" are the results of the investigations carried out by me at the "Centre for Brain Development and Research, inStem, NCBS, Bangalore" under the supervision of "Dr. Archana Purushotham" and the same has not been submitted elsewhere for any other degree.

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ABSTRACT

There are an increasing number of studies that are investigating how intrinsic (i.e. resting-state) functional connectivity correlates with cognitive abilities. However, our current understanding about the neural basis of inter-individual differences in cognitive abilities among healthy subjects is limited. Here we investigate correlation of MR-based intrinsic connectivity with multi-domain cognitive abilities in twenty-five healthy male subjects. Our results show that several cognitive abilities from different domains like music perception, empathy quotient, emotion recognition, mathematical abilities, logical reasoning, executive functions like working memory, response inhibition, fluency etc., attention, mental rotation tasks, motor speed, memory and language ability like comprehension, vocabulary, memory etc. are strongly positively correlated with each other. Connectivity within the task-negative network (TNN) is does not appear to correlate with test performance while connectivity within task positive networks (TPN) as also between TPN and TNN are correlated with test performance, suggesting that TPN connectivity, but not TNN connectivity, subserves inter-individual differences in cognitive abilities. Each cognitive test showed score correlation with specific Regions of Interest (ROI) pairs. Most of these ROIs have also been shown by previous studies to be activated by the respective tasks. Thus we show that even at rest, the functional architecture of the brain, and in particular of those regions invoked by the task, correlates with cognitive performance across a wide range of cognitive domains.

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INTRODUCTION

Cognition

The word cognition comes from the Latin verb cognōscō (con 'with' and gnōscō 'know') meaning 'to conceptualize' or 'to recognize'. It is defined as "the mental action or process of acquiring knowledge and understanding through thought, experience and senses" by the Oxford dictionary. Simply stated, cognition encompasses all higher mental functions such as attention, memory, reasoning, problem solving, decision making, musical abilities, empathy, emotion recognition, executive function, comprehension, production of language, etc. that we use in our daily life to undertake any task, simple to complex.

Deficits in various aspects of cognition underlie various neuro-psychiatric disorders like autism, multiple sclerosis, stroke etc. In order to pathophysiology of these disorders, it is important to understand the basis of cognition. Whether cognitive abilities are hereditary in nature or not remains a open question, though there have been attempts to answer this question (Devlin et.al., 1997).

Since the 19th century, numerous physicians like Franz Gall, Paul Broca etc. advocated the contribution of brain size to the variation in cognitive abilities. Since then several studies have been undertaken to support this theory. Some of the studies have talked about the correlation of some properties of the structure of the brain; like brain size (Rushton et.al., 1996), white matter architecture (Schmithorst et.al., 2005), regional brain structure (Johnson et.al.,2008), etc. with cognition. These studies were primarily done using imaging techniques like Magnetic Resonance Imaging (MRI) and Diffusion Tensor Imaging (DTI).

The focus by most of these studies has been on understanding the genetic or structural basis of cognition. However important property of these cognitive abilities is their plasticity. Even though structural and developmental changes can account for a part of this plasticity a large portion remains unexplained. In-spite of tremendous progress made in past couple of decades, there is a lot we do not understand about the basis of cognition. We are far from understanding the basis of cognitive abilities

in healthy and pathological conditions, forget discovering any panacea to neurological diseases. The next frontier in our quest to understand cognition comes from using functional magnetic resonance imaging techniques.

fMRI (functional Magnetic Resonance Imaging)

fMRI - functional magnetic resonance imaging uses the difference in magnetic properties of de-oxygenated hemoglobin (dHb), which is paramagnetic and oxygenated hemoglobin (Hb) which is diamagnetic in nature and the fact that neural activity is coupled with blood flow. In 1890, Charles Roy and Charles Sherrington first experimentally linked brain function to its blood flow, at Cambridge University . It was only in 1990 that this discovery found its amazing application in field of neuroscience. Seiji Ogawa discovered the MRI contrast of dHb known as the BOLD (Blood Oxygen Level Dependant) signal.

Following is a brief description of BOLD signal. In any inactive region of the brain there is usually a equilibrium in terms of amount of de-oxygenated hemoglobin and oxygenated hemoglobin. This balance is disturbed when neurons in a region become active. There is typically a increase in local blood flow with a lag of about couple of seconds. With new influx of blood there is a increase in proportion of oxygenated hemoglobin which rises to a peak for about 4-6 seconds. Then it falls down to the normal as oxygen is used up and the system returns to the original equilibrium state. There is a slight undershooting before final equilibrium is attained. As the Hb is diamagnetic it is virtually resistant to magnetism and interferes less with MR signal than dHb leading to a signal that looks like the following figure.

HDR = Hemodynamic Response Function
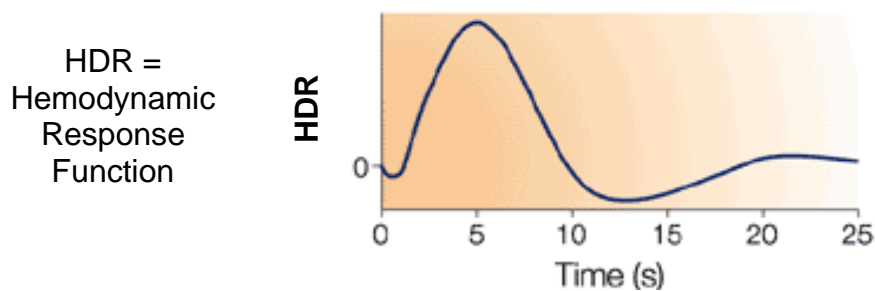
Fig.1 Hemodynamic Response Function

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There are two dimensions to recording a BOLD signal. One is the source of the signal and second is the evolution of the signal over time. Due to technical limitations we cannot record the BOLD signal from entire brain simultaneously over long period of time. There is a trade-off between the spatial resolution and the number of recordings of BOLD signal per unit time. One usually records a fMRI signal from same point in space every 1.5 - 3 seconds also known as the TR (Repetition Time). Depending on interest of researcher, one can choose to either scan the entire brain or just a portion of the brain. Usually the signal is recorded from small cubes (voxels) in the brain. The size of the voxel depends on the spatial resolution one desires to obtain in the recordings.

In order to facilitate recordings magnetic gradients are used. A gradient along Foot - Head typically helps divide the brain into slices for recording purpose. Signals are recorded from a single slice simultaneously; and every slice is recorded every unit TR. Two separate gradients in the anterior-posterior and right-left axis are used to obtain the x and y co-ordinates of the voxel location in space. BOLD signal in every voxel is recorded over a long period of time in order to obtain a time series evolution of the signal in a particular voxel. If there was cue presented that triggered neural activity and change in blood flow in the particular voxel "A" then one would expect a change in BOLD signal as shown in Fig.1 (Page 2).

If the cue was presented not just once but continuously for long stretch of time then the one would expect the hemodynamic response to be a convolution of single response. Now imagine a scenario, when a person was shown a visual cue for 30 seconds with a gap of 30 seconds. A voxel from the visual area could then be expected to have time-course like the following:

In Blue is the experimental visual stimulus of block design with cue every 30sec. and gap of 30sec.
In Green is the predicted Hemodynamic Response Function
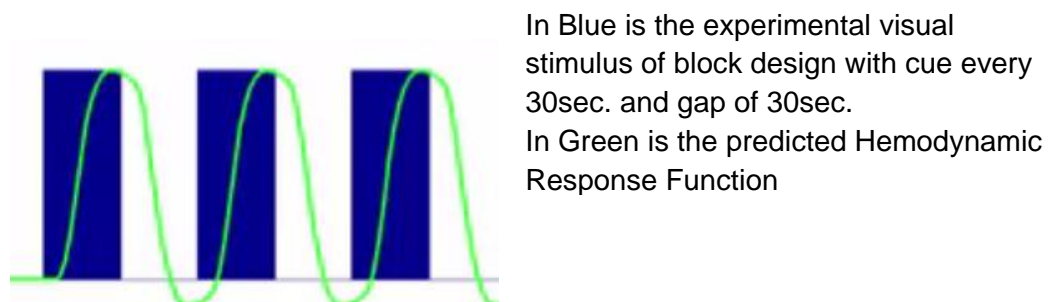
Fig.2 Predicted Hemodynamic Response Function for a block visual task

In reality the signal obtained in a voxel is typically noisy and following is actual image of time-series of signal in a voxel from occipital lobe during a visual task:
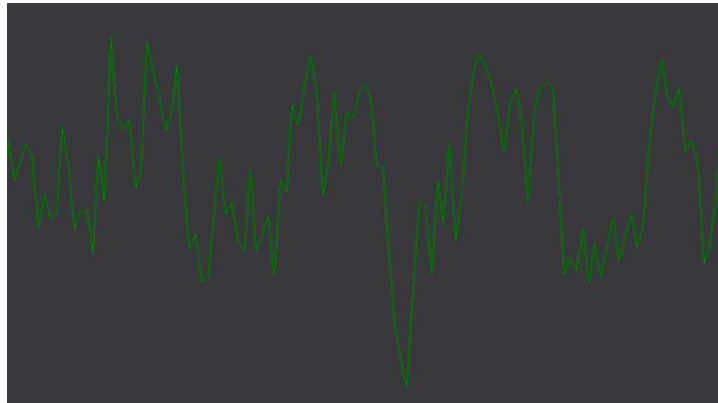
Fig.3 BOLD signal in a voxel from visual area during a block visual task

Using concepts of General Linear Modeling (GLM) one can obtain Z-thresholded maps which show all the voxels that were active during the task i.e. had a time-course that was strongly correlated with the time-course expected from a voxel involved in the task and the Z value is used to threshold. This is known as task-based fMRI. The following is a Z-thresholded image for visual task as described above.
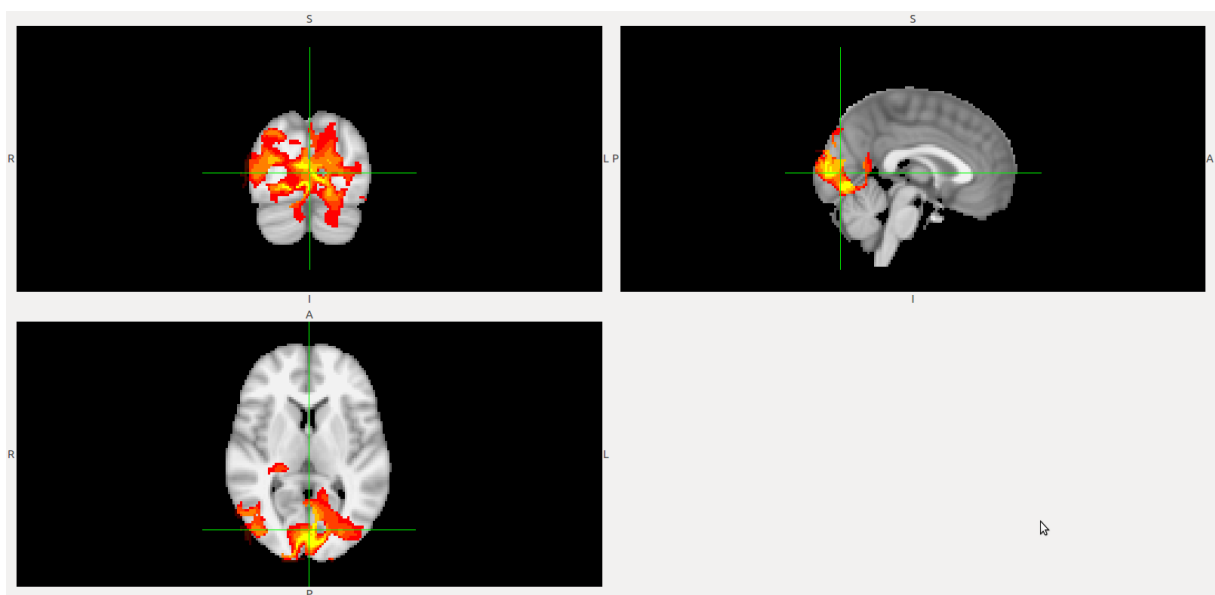
Fig.4 Z-thresholded image for a visual task showing localization in occipital lobe.

There is a vast amount of literature available for task-based fMRI studies, which correlate activity in certain region of the brain with performance in certain cognitive ability (Haier et.al.,2003; Gray et.al.,2003; Forstmann et.al., 2008). Though these

studies have helped open new avenues in understanding neural basis of cognition they have a major limitations, they assume localization of function in the brain. This localized view is fast losing audience as the idea that most higher cognitive functions are not completely localized and regions in brain act in consortium with one another i.e. a networks view gains popularity. Other problem is that these studies can only be performed on subjects capable of performing these tasks. There is growing enthusiasm for studying intrinsic functional connectivity to understand cognition better and bypass some of the limitations mentioned above.

Intrinsic Functional Connectivity

Functional connectivity(FC) is defined as "the statistical association or dependency among two or more anatomically distinct time-series" (Friston, K.J.,1994). Simply put, functional connectivity is determined by looking at correlation between time-series of any two voxels in any anatomical regions of the brain. Measures of FC are agnostic regarding causality or direction of connections. Functional connectivity has been studied in task evoked fMRI as well as resting state fMRI (rsfMRI)

Bharat Biswal showed that even during rest (while no task is being performed) the brain contains information about its functional organization. This was pioneering work on resting state fMRI. It is a method of functional brain imaging that can be used to evaluate regional interactions that occur when a subject is not performing an explicit task. There is extensive literature classifying these resting state functional connectivity networks also know as intrinsic connectivity networks (ICN). Some of the attractive features of ICN are as follows:

1. ICN networks are preserved during sleep and anesthesia (Fukunaga et.al., 2006; Greicius et.al., 2008).
2. They are fairly plastic, change during development (Fair et.al., 2008) and are likely to be shaped by genetic as well as environmental factors.
3. Intrinsic connectivity is likely to result not only from direct anatomical connections but also from multi-synaptic relationship,
4. Studies have demonstrated the structural basis of functional connectivity and shown that a lot of these intrinsic connectivity networks are similar to task evoked networks.(Smith et.al., 2009)

5. ICN can be easily studied not only in healthy subjects, but also in neonates, children, extreme pathological cases where it might not be possible to obtain task based fMRI.

Till now, there have been 9 resting state networks which are identified and classified as Default mode network (DMN), Executive control network, salience network, frontopareital network (FN), visual (Vi) network, auditory (Aud) network, sensorimotor (SM) network and amygdala network (Vaidya et.al, 2012; Smith et.al, 2009; Raichle, M.E., 2011; Damoiseaux et.al., 2006; Allen et.al., 2011; Van Dijk et.al.,2010)

Some of the methods available for studying resting state connectivity are:
1) Connectivity analysis between pairs of regions-of-interest (ROI)/ seeds
   The time-series of the BOLD signalfrom all the voxels within a defined region (atlas based or seed based ROIs) is averaged and then it is correlated with the averaged time-series of another region to obtain a pair-wise correlation values. The higher the absolute correlation value (could be positive/negative) the stronger is the connectivity while closer it is to zero the less likely they are to be connected.
2) Independent Component Analysis
   The ICA algorithm tries to partition the fMRI signal, based on the similarity in time-series of BOLD signal in voxels into a set of spatiotemporal components. ICA results in a set of maps in which each voxel is represented by a value equivalent to the likelihood of the voxel being part of that component.
3) Regional homogeneity (ReHo) Analysis
   The time-series of BOLD signal of a voxel is compared to its neighbours in order to obtain a correlation coefficient. A more homogenous activity in small region lead to a higher coefficient.
4) Graph theory analysis
   Brain regions are represented as nodes and connectivity between the regions as edges. Various network properties like centrality, clustering coefficient, path length, global efficiency, local efficiency, degree distribution, small worldness etc. are studied in this type of analysis.

A lot of studies have been undertaken to understand the changes in ICN in disease.There is growing evidence that changes in the strength of connectivity in networks underlie deficits seen in pathological conditions like autism (Belmonte et.al., 2004), multiple sclerosis (Mainero et.al., 2004), schizophrenia and depression (Hugdahl et.al., 2004) etc.

Connectivity and Cognition

Normal human subjects also show a large variability in cognitive abilities. It is unclear what the neural correlates of this normal inherent variability are.Inter-individual resting state connectivity between regions is also has a high variability (Mueller et.al., 2011). Some of the studies in recent years (Review of literature - Vaidya et.al., 2012) including ours, test the hypothesis that "the inherent variability in cognitive performance in normal human subjects is associated with differences in the intrinsic connectivity strengths."

Here is a summary of the studies that have looked at resting state functional connectivity and its correlation with cognitive abilities:

- Digit Backward (An executive domain task) score is positively correlated with connectivity within the salience network (Li et.al.,2012)
- Reading scores are positively correlated with the resting state connectivity between regions like Broca's area and Wernicke's area etc. (Hampson et.al.,2006)
- IQ (As measured by Wechsler adult intelligence scale - WAIS) is correlated with stronger connectivity within frontoparietal network (Song et.al., 2008) and ReHo within frontoparietal network, Parahippocampus, Inferior Lateral Temporal gyrus and Fusiform gyrus (Wang et.al., 2011).
- The ability to acquire arithmetic abilities in children can be predicted by hippocampal connectivity to dorsolateral and ventrolateral prefrontal cotices and basal ganglia, but not by IQ, pre-tutoring math ability or working memory scores (Supekar et.al.,2013).
- Left Hemisphere to Right Hemisphere connectivity is correlated with a total PANESS score (a battery designed for motor abilities) (Barber et.al, 2012).

A lot of these studies either look at a single cognitive ability like reading or use a more consolidated measure like IQ where multiple cognitive abilities are tested and

an overall score is obtained. Using a combined score like IQ decreases the resolution of the study. We will detect only connections that are correlated with multiple of the cognitive tests that are part of IQ, but lose out the signal from those which might have a strong correlation with only one or two cognitive domains, or might have inverse correlations with different domains. Some studies show that some of these cognitive abilities are correlated with each other; for instance, arithmetic, vocabulary and social translation are correlated with each other, as are rhythm, vocabulary and melody (Visser et.al., 2006). To investigate both across-domain and individual domain abilities, we chose to look at the neural basis of multi-domain cognitive abilities.

The aim of this study was to investigate the neural underpinnings of variations in multi-domain cognitive abilities like motor speed, attention, executive function, learning and memory, language, music, mathematical abilities, logical reasoning, visuo-spatial (mental rotation) abilities, social cognitive abilities like empathy and emotion recognition in healthy young adults in an Indian population. Due to established gender-based differences in brain connectivity patterns, we chose to restrict this study only to male subjects. The scope of this thesis was restricted to investigation of resting-state MR connectivity and its correlation with cognition. Task based fMRI activity/connectivity and structural connectivity might also provide an insight into the neural bases of cognitive abilities, but these were not investigated in this study.

MATERIALS & METHODS

Cognitive Battery design:

We developed a battery of 19 tests to assess cognitive abilities in multiple domains, appropriate for healthy normal adults in the Indian socio-cultural context. The battery is described in detail below:

Domain	Function	Test	Short Description / Reference
Speed	Motor	Finger Tapping (Motor_L and Motor_R)	The highest speed of 20 finger taps is recorded for right & left hand using a.bestmetronome.com.
	Mental	Symbol Digit Substitution (DSS)	Similar to letter digit substitution test (Elst et.al., 2006), but involves substituting for the digits 1 to 9 with 9 different symbols (instead of letters).
Attention		Bubble Trail	Modified version of the trail making test. (Reitan, R. M., 1958). The traditional trail making test involves two colours that one should alternate between while selecting numbers sequentially andwe added a third colour as an additional distracter.
Executive Function	Fluency	COWA - Oral Form (Fluency)	Benton controlled oral word association test (Ruff et.al., 1996).Total number of words person can recall in one minute starting from 'F', 'A', 'S' respectively. Category Fluency Test (Acevedo et.al., 2000). Total number of words person can recall in one minute each belonging to the following categories - animals and birds.
		Category Test	
	Working Memory	3- Back Test	This tests the ability to store and recall the last 3 out of a sequence of digits presented (Owen et.al., 2005)
	Response Inhibition	Stroop	3 Colour English version of the classic Stroop test. (Jenson et.al.,

			1966)
Learning and Memory		Word List (Memory)	60 words were shown to subjects for 2 seconds each. The task was free recall: to recall as many words as possible.
Logic		Questionnaire	The ability to solve logical problems, make logical deductions etc. was tested.
Language		Vocabulary Questionnaire (Vocab)	The types of questions are: give one word for, anagrams, jumbled words, &analogies.
		Comprehension (Compre)	Subjects were given a long passage with 5 minutes to read & understand; then they were asked factual & non-factual questions based on the passage.
Mathematical Abilities		Questionnaire (Math)	The questionnaire was designed to test basic mathematical skills.
Musical Abilities		Musical Ear Test (MET) – Melody & Rhythm	This test requires listeners to listen to short melodic, or rhythmic phrases, and decide if pairs of phrases are exactly similar or subtly different.(Wallentin et.al., 2010)
Visuo-Spatial Abilities	Mental Rotation	Questionnaire (Visuo-spa)	The ability of subjects to perform mental rotations of objects and general 2D and 3D visuo-spatial abilities was tested.
Social Cognition	Empathy Quotient (EQ)	ARC Questionnaire	This test was taken from the Autism Research Centre (ARC) website (Lawrence et. al. ,2004)
	Emotion Recognition	ARC Eyes Test	This test was taken from (ARC) too. (Richell et. al. ,2003)

Table 1. Cognitive Assessment Battery Details.

Normative Data - Cōgitāre Website designing

As normative data for cognitive abilities across multiple domains in healthy adults in India is not available, we created a website http://cogitare.instem.res.in/(Cōgitāre) for collecting normative data containing most of the above mentioned tests. The major

part of designing this website was done by one of the summer students in the lab (Harini Suri).

Inclusion criteria for normative data were as follows :
1. Subjects should be 21 - 55 years old.
2. Subjects should be college educated in India.
3. Subjects should have completed Bachelor's degree or equivalent.
4. Subjects should have sufficient fluency in English.

The inclusion criteria were decided in order to ensure uniformity in knowledge of basic arithmetic and language. This data was scored using codes written in Python. The results of these have not been presented in the thesis. However, these helped in ensuring that none of the tests showed a ceiling effect and we were obtaining a wide enough distribution of these scores.

Enrolment of subjects for the main study:
Subjects were recruited through fliers posted on academic campuses, word of mouth and through social networking sites and e-mailing lists.
Inclusion criteria:
1. Age: 25 - 35 years
2. Education: college educated in India with completed 3-year Bachelor's degree or equivalent.
3. Fluent in English.

Exclusion Criteria:
1. Contra-indications to, or inability to cooperate with, MRI
2. History of neurological or psychiatric disorders or head trauma leading to loss of consciousness

The inclusion and exclusion criteria aimed to ensure uniformity in knowledge of basic mathematics and language, ensure completion of neurodevelopment and exclude potential effects of neurodegenerative processes. Our study was approved by the concerned Institutional Ethics Committee and all the subjects provided written

informed consent. In addition to obtaining medical history and demographic information, we recorded the handedness of the subjects.

Administration of cognitive battery

The battery was administered to subjects in two testing sessions on two separate days to avoid fatigue associated artefacts in performance. Breaks were provided after each test in each session, as needed. Subjects were requested to follow their usual schedules and not prepare anything in particular for the tests. They were also requested to inform us in case they experienced any fatigue, anxiety, stress or any other health related problems, to ensure this did not affect recorded scores .

All except the MET were administered using an offline version of Cōgitāre. The MET was administered on paper. The fluency, category and memory recall tests. were audio recorded for ease of scoring. Motor tapping speed was recorded using the free online metronome at a.bestmetronome.com

fMRI scan

The fMRI scan was obtained using a SIEMENS SKYRA 3Tesla MR scanner at HCG Hospital, Bangalore. Cognitive testing and MRI scanning for 25 healthy adult male subjects who satisfied the inclusion and exclusion criteria was completed.

Scanning Protocol

We obtain structural images with following parameters:

Series Description	T1-weighted	TE (Echo Time)	3.9 m.sec
No. of Slices	192	TR (Repetition Time)	8.3 m.sec
Slice Thickness	1mm	Flip Angle	90 °
Distance factor	20%	Phase Encoding	Anterior>>Posterior
FOV (Field of View)	240*240	Duration	4min 38 sec.

Table.2 Parameters for Structural Scan

We further obtained resting state scans, functional localizers and DTI images. During the resting state scans, the subjects were requested not to think hard, or for

prolonged periods about anything. Resting state scans were obtained while subjects were awake with their eyes closed. Following are the parameters used for the fMRI Scans (resting state and functional localizers):

Series Description	Echo planar Imaging (BOLD)	TE	30 m.sec
No. of Slices	26	TR	2000 m.sec
Slice Thickness	5mm	Flip Angle	90 °
Distance factor	10%	Phase Encoding	Anterior>>Posterior
Sequence Order	Interleaved	Total no. of	240 (Resting-State)
FOV	240*240	scans	125 (functional localizer)

Table.3 Parameters for Functional Scan

Functional Localizers

There were 6 functional localizer sequences consisting of the following tasks/stimulus paradigms: Visuo-motor, Language, 3Back (Drobyshevsky et.al.,2006), math, emotion and memory. The final analysis based on functional localizers could not be done during this dissertation period due to time limitations, hence although the paradigms were designed and acquired, this data will be used only in future analyses.
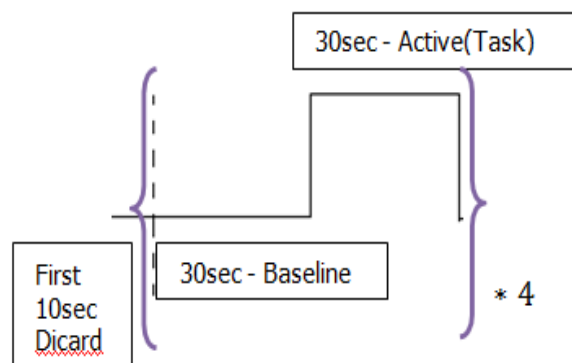
Fig.5 Design summary for functional localizer.

Cognitive Test Scoring

A Python based script was written to determine the score and time taken by each subject in each test. Performance over the time-course of the test was checked to ensure subjects did not lose interest midway, and genuinely attempted to answer all

questions to the end. Scores for time-sensitive tests were calculated by weighting the raw score with time taken. The equation used to calculate weighted scores for Stroop, Symbol Digit Substitution and 3-Back test was :

$$\frac{Number of right answers \times \frac{Average time taken by all subjects}{Time taken by particular subject}}{Total No. of Questions}$$

In case of Bubble trail, the score was simply calculated as

$$\frac{Average time taken by all subjects to complete trail}{Time taken by the particular subject}$$

For math and logic the score was not only weighted by time taken per question, but also scaled by number of questions.

$$\frac{\sum_{all correct questions} \frac{Average time taken for the question by all subjects who got it right}{Time taken for the question by the particular subject}}{Total No. of Questions}$$

For comprehension and visuo-spatial tests, the score obtained was divided by the total no. of questions on the test. Motor speed was obtained in the units of Beats per minute (BPM) and was scaled in following manner: assuming 300 BPM represented an arbitrary 'slowest' and 650 BPM a similar 'fastest' finger tapping speed:

$$\frac{Motor speed\ (in BPM)\ for the subject - 300}{650 - 300}$$

Pearson's correlation coefficient was calculated for each test pair using the scaled scores yielded by the formulae above. A heat map was generated using these correlation coefficients. This was done using python module matplotlib. A hierarchical clustering analysis was performed on these tests using WGPMA method to obtain a dendrogram showing the relationship of these tests with each other. The distance matrix was calculated using Euclidean distance scaled by variance. This was done using the scipy module in python. We attempted to verify the similarity patterns between our tests using a second clustering method - k-means clustering – in Matlab, to separate these tests into 5 clusters

Connectivity Analysis

Preprocessing Pipeline for resting state connectivity analysis

CONN, a SPM(Statistical Parametric Mapping) based toolbox was used for all steps of pre-processing except for manual reorientation which was done using SPM 12. The steps involved in pre-processing were:

1. Slice-time correction: This is done in order to correct for the difference in the acquisition time of each slice.

2. Manual re-orientation in SPM: This is a preliminary step to bring the subject scan into a similar orientation with respect to the template scan, before performing automated co-registration..

3. Realignment of functional images: This step is crucial for minimizing the effects of subject motion during functional scans. It ensures that every volume is aligned well with the other. Realignment was done with respect to the mean volume. Motion covariates are also obtained in this step, to use as potential nuisance regressors in later steps of analysis.

4. Co-registration of functional volumes to structural image: The structural and functional images of the subject are brought into alignment with each other.

5. Segmentation and Normalization of structural images: The structural image is segmented to give grey matter, white matter and CSF images. These are required for further analysis. White matter and CSF images are used in de-noising step while Grey matter image is used as a mask to obtain subject specific ROIs. In normalization, the images obtained for each subject are co-registered with a standard template image so that all subjects' images can be overlaid onto each other, and group analyses performed. We decided to use the MNI brain template (need reference) for which brain atlas and co-ordinate based labeling are easily available.

6. Normalization of functional images: The functional images are also similarly normalized.

De-noising for resting state connectivity analysis

White matter, Cerebrospinal Fluid (CSF), motion were used as first-level covariates. These were regressed out in this step. De-noising of the data was done using linear detrending and using a band-pass filter from 0.008 Hz to 0.1Hz in order to remove

frequencies that are not of interest and improve signal to noise ratio. De-noising was carried out in CONN.

First level analysis for resting state connectivity

Resting State Networks - ROI based

> We decided to focus on the known resting state or intrinsic connectivity networks (ICN's) - Default mode network (DMN), Executive control network, salience network, frontoparietal network, visual network, auditory network, somatosensory network and amygdala network. (Vaidya et.al, 2012; Raichle, M.E., 2011; Allen et.al.,2011; Van Dijk et.al.,2010) Using these referenced articles, we shortlisted 56key nodes of these networks. From the AAL atlas, we picked a few ROIs that could not be subdivided into multiple nodes. For the rest of the ROIs, we used MNI coordinates (Allen et.al.,2011; Raichle, M.E., 2011) and created spheres of radius 7mm-9mm using WFU pick-atlas, a MATLAB based software. The following is a list of ROIs that we chose for this analysis:

RSN name	Area Name	MNI Coordinates			Reference
		X	Y	Z	
Default mode network (DMN)	Medial Prefrontal Cortex (MPFC)	-1	45	-9	Allen et.al., 2011
	Precuneus (PC)	0	-63	43	
	Angular Gyrus Left (AG_L)	-42	-69	33	
	Angular Gyrus Right (AG_R)	47	-66	33	
	Posterior Cingulum, (Post_Cing)	0	-52	22	
Attention + Salience + Executive (ASE)	Middle Frontal Gyrus Left (MFG_L_1)	-27	24	44	Allen et.al., 2011 & Raichle, M.E.,2011 (dACC)
	MFG_L_2	-25	1	60	
	MFG_L_3	-32	53	21	
	MFG Right (MFG_R_1)	34	24	49	
	MFG_R_2	26	0	60	
	Precuneus	0	-53	61	
	Superior Temporal Gyrus (STG_L_1)	-62	-2	0	
	STG_L_2	-56	-48	18	
	STG_R_1	57	-44	11	
	STG_R_2	58	0	2	
	Angular Insula Left	-44	15	-5	
	Angular Insula Right	44	18	-6	
	Inferior Parietal Lobe (IPL_L)	-48	-54	40	

Network	Region	x	y	z	Atlas
	IPL_R	46	-55	39	
	Anterior Cingulate (dACC)	0	21	28	
	Superior Parietal Lobe (SPL_L)	-27	-65	44	
	SPL_R	27	-65	44	
Frontal network (FN)	Supramarginal Gyrus (SMG_L)	-58	-36	36	Allen et.al., 2011 & Van Dijk et.al.,2010 (MTG)
	SMG_R	58	-36	36	
	Middle Frontal Gyrus Left (MFG_L_1)	-48	21	29	
	MFG_L_2	-31	52	8	
	MFG Right (MFG_R_1)	49	22	25	
	MFG_R_2	31	55	7	
	Inferior Frontal Gyrus Left (IFG_L_1)	-42	39	5	
	IFG_L_2	42	39	5	
	IFG Right (IFG_R_1)	-55	22	7	
	IFG_R_2	55	22	7	
	Dorsal MPFC (dMPFC)	0	32	46	
	Middle Temporal Gyrus (MTG_L)	-56	-60	-2	
	MTG_R	56	-60	-1	
Auditory network	Heschl's gyrus (HG_L) HG_R				AAL atlas
Basal Ganglia	Putamen_L Putamen_R				AAL atlas
Sensori-motor Network (SM)	Supplementary Motor Area (SMA_L), SMA_R, Precentral_L, Precentral_R Postcentral_L, Postcentral_R				AAL atlas
Amygdala network (Amy)	Amygdala_L, Amygdala_R Hippocampus_L, Hippocampus_R Parahippocampus_L (PHC_L), PHC_R				AAL atlas
Visual network (Vi)	Calcarine	-29	-76	-8	AAL atlas (calcarine) & Allen et.al.,2011
	Lingual_L	29	-76	-8	
	Lingual_R	-47	-63	-12	
	Inferior Temporal Gyrus (ITG_L)	48	-63	-12	
	ITG_R Cuneus	2	-82	24	

Table.4 Details about the ROIs used in analysis

Using these ROIs we obtained subject-wise, ROI-wise BOLD signal time-courses from CONN toolbox post-denoising.

Connectivity Calculation

To obtain connectivity between any two ROI-pairs we used Kendall's correlation coefficient to correlate time-series from each of the ROI. We thus obtain a matrix containing connectivity values for 1540 unique ROI pairs for each of the subjects. This matrix was used for further analysis. This computation was done using numpy module in python.

Score - Connectivity Correlation Analysis Statistics

Each of the ROI pairs connectivity values was correlated with each of the 18 test-scores using Kendall's correlation coefficient. The results have been presented in the following section using graphical representations generated using Python and several of its free modules like numpy, matplotlib, scipy, imshow, pyplot etc.

RESULTS

1) Test Scores

Our test subjects were all college educated but we saw a reasonable degree of variance in test scores, confirming that our test battery was successful in capturing some of the variance in cognitive abilities among the normal population. Here is an example of a histogram showing the score distribution in our cohort.
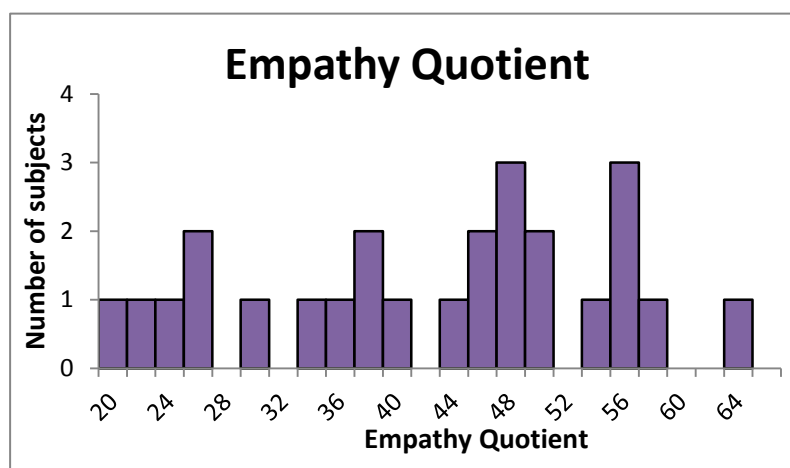
Fig.6 Histogram for distribution of Empathy Quotient

There are known connectivity differences between right and left dominant people. Thus the following data is presented for only 23 subjects who were right-handed i.e. excluding 2 left handed subjects. Scores were scaled and weighted as explained in the Methods section. All the results are based on using scaled weighted scores. The std. deviation, minimum and maximum scaled scores for each test are tabulated below:

Test name	Min. Score	Max. Score	Std. Dev	Test name	Min. Score	Max. Score	Std. Dev
3Back	0.425	1.762	0.359	Math	0.093	1.500	0.347
DSS	0.689	1.222	0.126	Visuo-spatial	0.200	1.000	0.198
Stroop	0.390	1.669	0.304	Fluency Test	0.133	0.800	0.161
Music (Melody)	0.462	0.923	0.104	Motor Speed (Right)	0.169	0.877	0.162
Music (Rhythm)	0.596	0.885	0.080	Motor Speed (Left)	0.060	0.683	0.191
EQ	0.250	0.788	0.154	Category Test	0.233	0.867	0.138
Eyes	0.500	0.889	0.117	Memory	0.117	0.700	0.183
Language	0.040	0.600	0.164	Bubble-Trail	0.565	1.737	0.327
Logic	0.234	1.837	0.315	Comprehension	0.133	0.667	0.160

Table.5 Statistics related to test scores like std. deviation,
maximum and minimum in test scores.

2) Inter-cognitive abilities correlation

Fig. 7 represents a heat map showing correlations between test scores. All correlations with p-uncorrected<0.05 were positive.
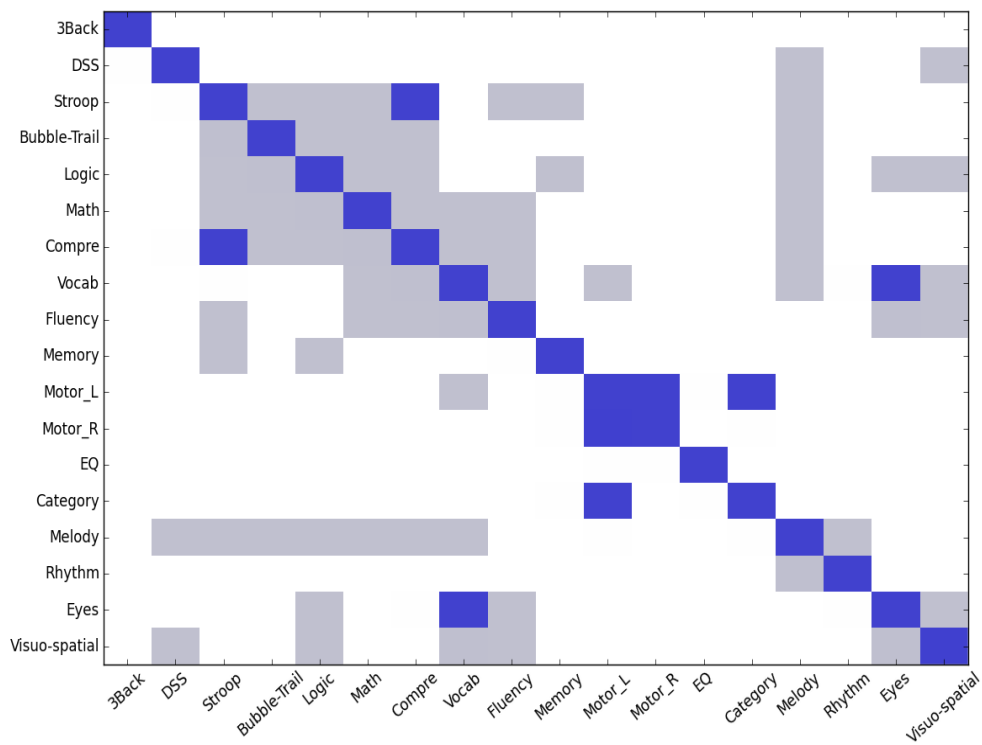
Fig.7 Heat map of Kendall's correlation coefficient between scores obtained on different tests in our cognitive battery. Only areas with a p (uncorrected) < 0.05 are indicated. Light blue : Correlation coefficient 0.2-0.5
Dark blue: Correlation coefficient > 0.5

2) Clustering of Cognitive Abilities

As there are strong correlations between many of the cognitive tests, we performed cluster analysis to identify patterns of relatedness among the tests. First we used hierarchical clustering to obtain the following dendrogram.

Fig 8 Dendrogram based on hierarchical clustering of cognitive tests based on Euclidean distance
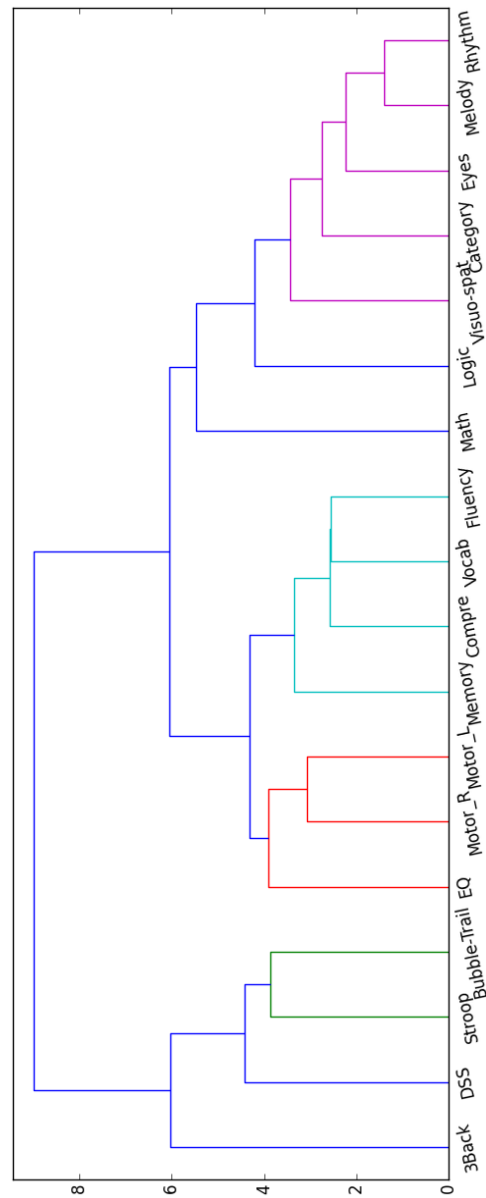
K-means clustering also yielded similar results. The 5 clusters obtained were as follows:

Cluster 1 : 3Back, DSS, Stroop and Bubble-trail

Cluster 2 : Comprehension, Vocabulary, Fluency, Memory and Motor_L

Cluster 3 : Melody, Rhythm, Visuo-spatial and Eyes

Cluster 4 : Logic and Math

Cluster 5 : Motor_R, Category and Empathy Quotient

3) Test-wise Correlation of Scores and Connectivity (Network Level)

Within TNN (DMN)
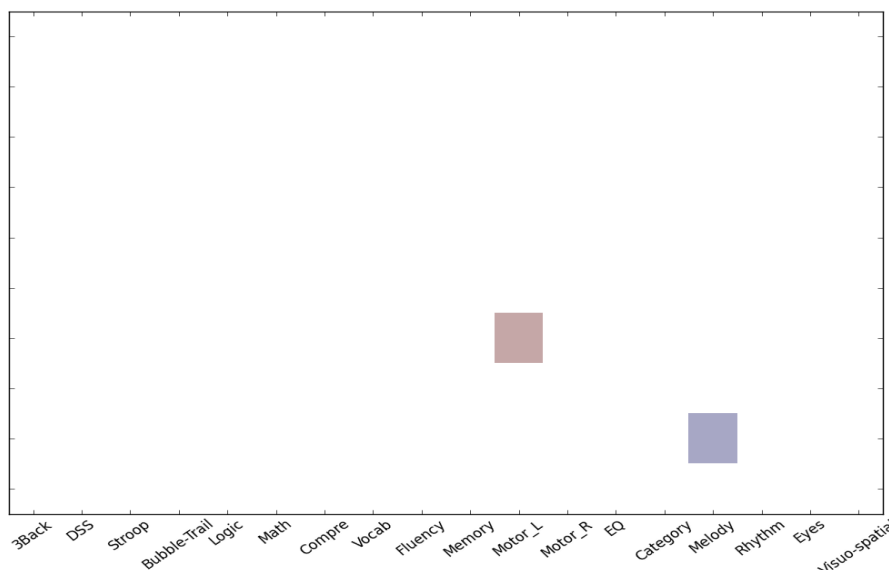
Fig.9 Heat map of correlation between connectivity within DMN, and test scores. Only areas with a p-uncorrected<0.05 are indicated. Blue is for positive correlation and red for negative. At a p-uncorrected < 0.01 threshold, no ROI pairs show significant correlations.

Between TPN-DMN
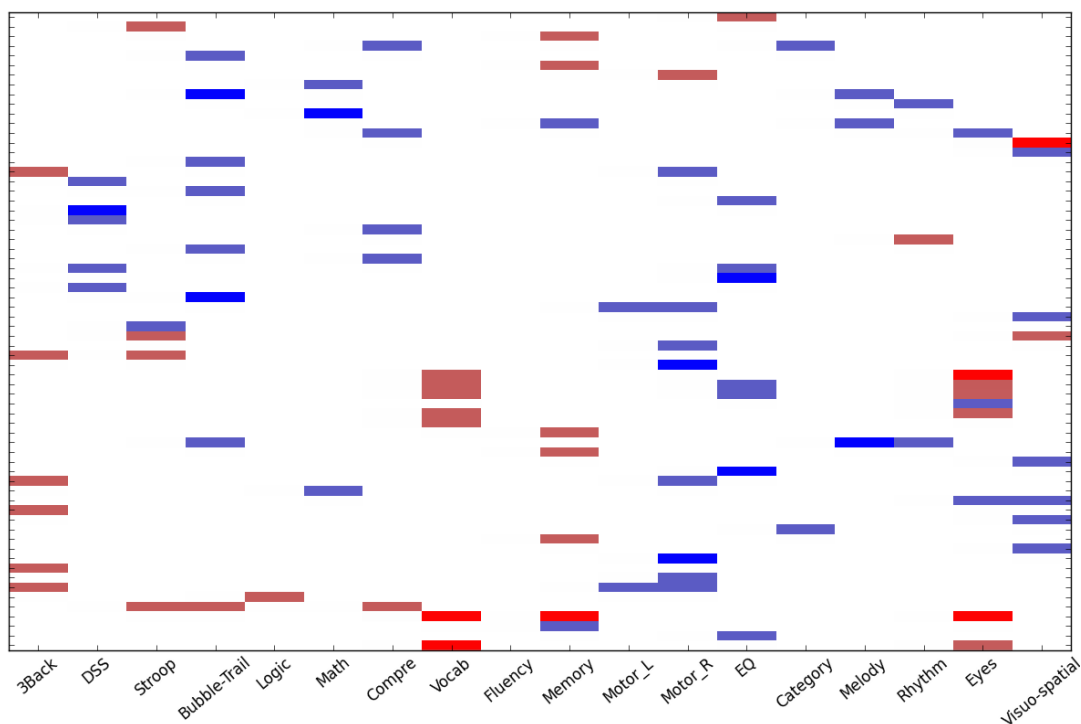
Fig.10 Heat map of Kendall's correlation coefficient between connectivity and test scores. Only areas with a p-uncorrected<0.05 are indicated. Blue is for positive correlation and red for negative. p<0.05 is lightest shade, p<0.01 is a brighter shade of the respective color.

Within TPN

Fig.11 Heat map of Kendall's correlation coefficient between within TPN connectivity and test scores. Only areas with a p-uncorrected<0.05 are indicated. Blue is for positive correlation and red for negative. p<0.05 is lighter shade, p<0.01 is brighter shade of the respective color.
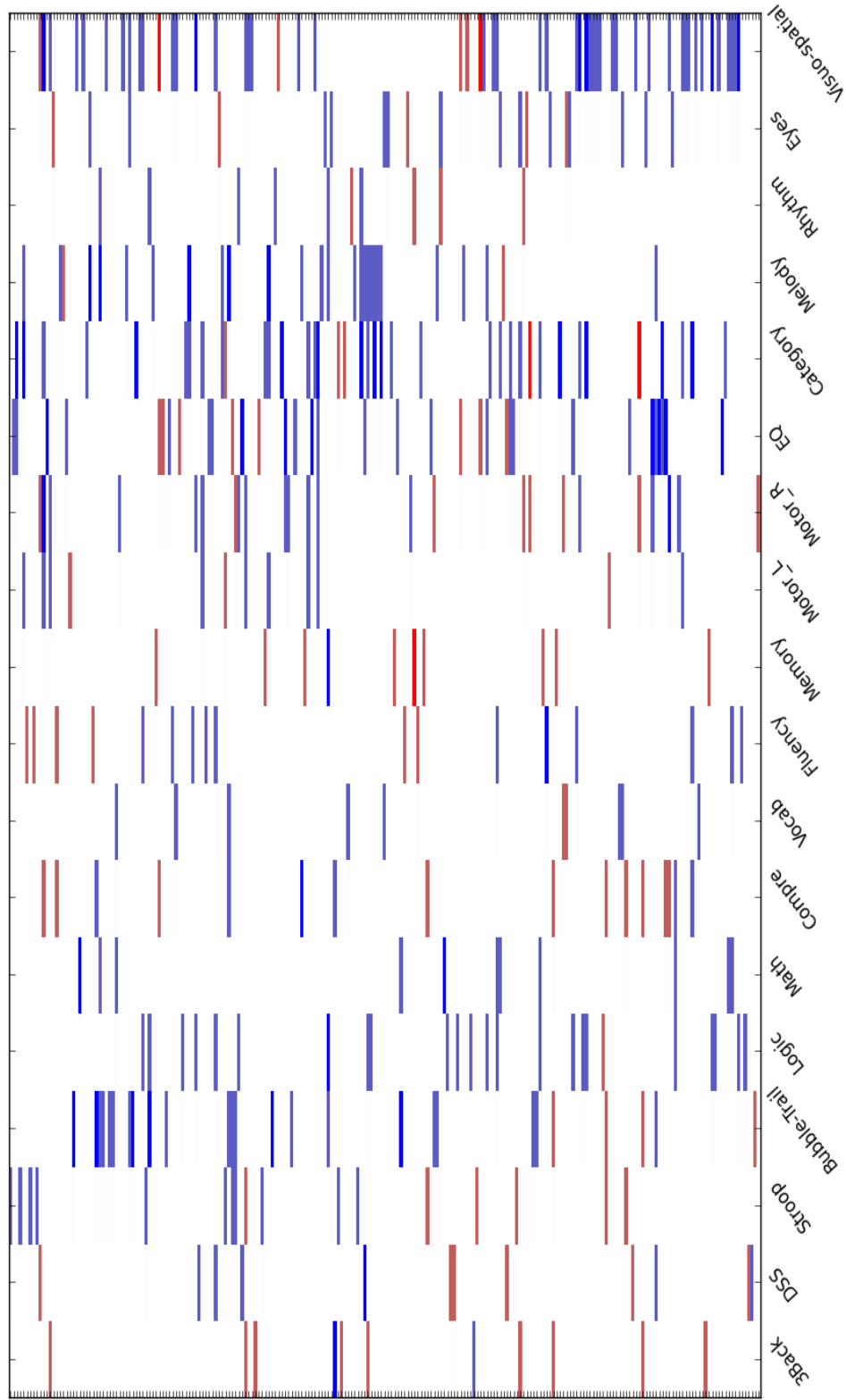
3) Test-wise Correlation of Scores and Connectivity (Pair-wise)

Test name	Kendall's R	Kendall's P	ROI-pair Name
3Back	-0.462	0.002001	Amy_PHC_R-Vi_ITG_R
	-0.423	0.004715	Amy_Hippo_R-Vi_Lingual_R
	-0.407	0.006523	ASE_STG_2_R-Vi_ITG_R
	-0.391	0.008932	Amy_Hippo_R-Vi_ITG_R
DSS	-0.448	0.002778	MTG_L-SM_Postcentral_L
	0.432	0.003933	ASE_ACC-Amy_Amygdala_L
	0.415	0.005509	dmn_AG_L-ASE_MFG_1_R
	-0.407	0.006493	Vi_ITG_L-Vi_Cuneus_Bi
	0.399	0.007633	FN_MFG_1_R-Amy_Amygdala_L
Stroop	0.417	0.005367	ASE_PC_Bi-ASE_STG_2_R
	0.409	0.006312	ASE_MFG_1_R-Vi_ITG_R
	0.393	0.008664	FN_IFG_1_L-Vi_ITG_R
Bubble-Trail	0.486	0.00116	dmn_PCC-ASE_IPL_L
	0.486	0.00116	ASE_IPL_L-ASE_IPL_R
	0.486	0.00116	ASE_MFG_2_L-ASE_SPL_R
	0.486	0.00116	ASE_SPL_R-SM_Precentral_L
	0.486	0.00116	ASE_STG_2_R-BG_Putamen_L
	0.439	0.003373	ASE_IPL_L-ASE_SPL_R
	0.423	0.004715	ASE_IPL_L-FN_SMG_R
	0.423	0.004715	ASE_IPL_R-ASE_MFG_2_L
	0.423	0.004715	ASE_IPL_R-SM_Precentral_R
	0.423	0.004715	BG_Putamen_L-Amy_PHC_R
	0.407	0.006523	dmn_AG_R-BG_Putamen_L
	0.407	0.006523	ASE_IPL_L-SM_Postcentral_L
	0.407	0.006523	ASE_SPL_R-SM_Precentral_R
	0.407	0.006523	FN_IFG_1_L-Amy_PHC_L
	0.407	0.006523	BG_Putamen_L-Aud_HG_R
	0.399	0.007643	FN_SMG_R-BG_Putamen_L
	0.391	0.008932	dmn_PCC-BG_Putamen_L
	0.391	0.008932	ASE_IPL_L-Vi_Calcarine_Bi
	0.391	0.008932	ASE_IPL_R-SM_Precentral_L
	0.391	0.008932	ASE_SPL_R-BG_Putamen_L
	0.391	0.008932	BG_Putamen_L-Amy_Amygdala_R
Logic	0.462	0.002001	ASE_MFG_3_L-Amy_Amygdala_L
	-0.447	0.002842	MTG_R-Vi_Lingual_L
	0.431	0.003993	ASE_aInsula_R-Amy_PHC_R

	0.415	0.005553	ASE_ACC-Amy_Amygdala_L
	0.407	0.006523	ASE_MFG_3_L-FN_IFG_1_L
	0.407	0.006523	FN_IFG_1_R-Vi_ITG_R
Math	0.423	0.004715	dmn_PCC-ASE_MFG_1_R
	0.423	0.004715	SM_Precentral_R-Amy_Amygdala_R
	0.407	0.006523	ASE_IPL_R-BG_Putamen_R
	0.399	0.007643	dmn_PCC-FN_MFG_2_R
	0.391	0.008932	ASE_IPL_L-ASE_MFG_1_R
	0.391	0.008932	ASE_SPL_R-FN_MFG_2_R
Compre	0.420	0.005004	Vi_Calcarine_Bi-Vi_ITG_L
	0.403	0.007049	ASE_MFG_2_R-Vi_Calcarine_Bi
	-0.403	0.007049	ASE_STG_2_R-Vi_Lingual_L
	0.403	0.007049	Vi_Lingual_R-Vi_ITG_L
	0.395	0.00833	ASE_MFG_2_R-ASE_PC_Bi
	-0.395	0.00833	ASE_STG_1_R-Amy_Hippo_R
	-0.395	0.00833	Vi_Calcarine_Bi-Vi_ITG_R
	0.395	0.00833	Vi_Calcarine_Bi-Aud_HG_L
	-0.386	0.009816	ASE_STG_2_R-Amy_Hippo_R
	-0.386	0.009816	Vi_Lingual_R-Vi_ITG_R
Vocab	0.520	0.000508	Vi_ITG_L-Vi_ITG_R
	0.456	0.002325	FN_MFG_1_R-Amy_PHC_L
	-0.407	0.006493	dmn_MPFC-FN_dMPFC
	0.399	0.007633	MTG_L-Amy_PHC_L
	-0.391	0.008949	dmn_MPFC-FN_IFG_2_L
	0.391	0.008949	MTG_L-Vi_ITG_R
Fluency	-0.481	0.001309	FN_dMPFC-Vi_Lingual_L
	-0.441	0.003217	ASE_MFG_1_R-Vi_Lingual_L
	-0.441	0.003217	FN_MFG_1_R-Vi_Lingual_L
	-0.393	0.00867	ASE_SPL_L-Amy_Amygdala_R
Memory	-0.490	0.001059	ASE_SPL_L-FN_IFG_2_R
	0.466	0.001841	ASE_IPL_R-Amy_Amygdala_R
	-0.458	0.002202	dmn_MPFC-FN_IFG_2_L
	-0.458	0.002202	FN_IFG_2_R-Vi_ITG_L
	-0.426	0.004392	FN_IFG_2_R-Vi_Lingual_L
	0.410	0.006106	ASE_MFG_3_L-FN_IFG_1_L
	0.410	0.006106	FN_SMG_R-Amy_Amygdala_R
	-0.402	0.007171	ASE_SPL_L-Vi_ITG_L
	-0.402	0.007171	FN_MFG_2_L-Vi_ITG_L
	-0.402	0.007171	SM_SMA_L-Vi_Lingual_L

Category	Value	p-value	Connection
	-0.394	0.0084	ASE_MFG_1_L-Vi_Lingual_L
	-0.394	0.0084	FN_IFG_1_R-Vi_Lingual_L
	0.394	0.0084	FN_MFG_2_L-BG_Putamen_L
	0.386	0.009814	Amy_Amygdala_R-Vi_Cuneus_Bi
Motor_L	-0.401	0.007405	ASE_STG_2_R-SM_Precentral_R
	-0.464	0.00192	Amy_Hippo_L-Amy_PHC_L
	0.448	0.002733	FN_IFG_1_R-FN_MFG_1_R
	0.448	0.002733	FN_IFG_1_R-SM_Precentral_L
	0.440	0.003248	dmn_AG_R-ASE_aInsula_R
Motor_R	0.425	0.004552	ASE_ACC-ASE_aInsula_R
	-0.425	0.004552	ASE_STG_2_L-SM_Postcentral_L
	0.401	0.007405	FN_IFG_1_R-Amy_Amygdala_R
	0.393	0.008664	ASE_aInsula_R-BG_Putamen_R
	0.393	0.008664	FN_IFG_1_R-SM_Postcentral_L
	0.506	0.000722	ASE_MFG_2_R-FN_IFG_1_L
	0.474	0.001535	FN_MFG_1_R-FN_dMPFC
	0.466	0.001841	FN_IFG_1_L-SM_SMA_R
	0.450	0.002628	ASE_MFG_1_R-FN_IFG_1_L
	0.442	0.003127	ASE_MFG_2_L-FN_IFG_1_L
	0.434	0.003711	SM_SMA_L-SM_Precentral_R
	0.426	0.004392	FN_IFG_1_L-FN_dMPFC
	0.418	0.005185	ASE_MFG_1_R-Amy_Amygdala_L
	0.418	0.005185	FN_IFG_1_L-FN_MFG_1_R
	0.410	0.006106	FN_IFG_1_R-FN_IFG_2_R
	0.410	0.006106	FN_dMPFC-Amy_Amygdala_L
EQ	0.402	0.007171	dmn_AG_L-ASE_STG_2_R
	0.402	0.007171	ASE_ACC-FN_IFG_1_L
	0.402	0.007171	FN_IFG_1_L-SM_SMA_L
	0.402	0.007171	FN_IFG_1_L-SM_Precentral_R
	0.402	0.007171	FN_IFG_1_L-Amy_Amygdala_R
	-0.402	0.007171	MTG_R-Amy_Hippo_L
	0.402	0.007171	SM_SMA_L-SM_SMA_R
	0.394	0.0084	ASE_MFG_2_R-Amy_Amygdala_L
	0.394	0.0084	FN_IFG_1_L-SM_Postcentral_R
	-0.386	0.009814	ASE_IPL_R-SM_Precentral_R
	-0.386	0.009814	ASE_SPL_R-SM_Precentral_R
	0.386	0.009814	SM_SMA_L-Amy_Amygdala_R
	0.569	0.000145	dmn_MPFC-BG_Putamen_L
Category	0.504	0.000756	ASE_PC_Bi-FN_dMPFC
	0.448	0.002778	ASE_MFG_2_R-SM_SMA_L

	0.448	0.002778	ASE_MFG_2_R-SM_Precentral_L
	0.448	0.002778	SM_SMA_L-SM_SMA_R
	0.432	0.003933	ASE_aInsula_R-SM_SMA_R
	0.423	0.004661	ASE_aInsula_L-FN_MFG_2_R
	0.423	0.004661	FN_IFG_1_R-FN_IFG_2_L
	0.407	0.006493	ASE_ACC-ASE_MFG_2_R
	0.407	0.006493	ASE_ACC-Amy_Amygdala_R
	0.407	0.006493	SM_SMA_L-SM_Precentral_R
	0.399	0.007633	dmn_AG_L-Amy_PHC_L
	0.399	0.007633	ASE_IPL_L-FN_dMPFC
	0.399	0.007633	ASE_MFG_2_L-ASE_aInsula_R
	0.399	0.007633	ASE_PC_Bi-ASE_aInsula_R
	0.391	0.008949	ASE_ACC-ASE_PC_Bi
	0.391	0.008949	ASE_MFG_2_R-FN_dMPFC
	0.391	0.008949	ASE_MFG_2_R-SM_SMA_R
	0.391	0.008949	ASE_aInsula_R-FN_dMPFC
	0.595	6.96E-05	ASE_MFG_1_R-ASE_PC_Bi
	0.498	0.000874	ASE_PC_Bi-SM_SMA_L
	0.482	0.001281	ASE_IPL_L-ASE_PC_Bi
	0.458	0.00223	dmn_PC-FN_MFG_2_R
	0.458	0.00223	ASE_PC_Bi-SM_SMA_R
Melody	0.450	0.002668	ASE_ACC-Amy_Amygdala_L
	0.425	0.004493	ASE_MFG_1_L-ASE_PC_Bi
	0.417	0.005317	ASE_MFG_2_L-ASE_PC_Bi
	0.401	0.007386	FN_IFG_1_L-Amy_PHC_L
	0.401	0.007386	FN_dMPFC-Amy_Amygdala_L
	0.393	0.00867	ASE_MFG_1_R-Amy_PHC_L
	0.409	0.006275	dmn_MPFC-Amy_Hippo_L
	0.409	0.006275	FN_dMPFC-Vi_Cuneus_Bi
	-0.401	0.007386	FN_SMG_L-Aud_HG_L
Rhythm	-0.401	0.007386	Amy_PHC_L-Aud_HG_L
	0.393	0.00867	FN_SMG_R-Aud_HG_R
	0.393	0.00867	FN_dMPFC-Amy_Hippo_L
	-0.393	0.00867	Amy_PHC_L-Vi_ITG_L
	0.505	0.000744	ASE_STG_2_L-Vi_Calcarine_Bi
	0.488	0.00112	ASE_IPL_L-SM_Precentral_R
	0.436	0.003551	ASE_STG_2_L-Vi_Lingual_R
Eyes	-0.428	0.004259	dmn_MPFC-ASE_MFG_1_L
	0.428	0.004259	ASE_STG_2_L-Vi_ITG_R
	0.419	0.005092	MTG_L-Vi_Calcarine_Bi
	0.411	0.00607	MTG_L-Vi_Cuneus_Bi

	-0.402	0.007214	dmn_MPFC-FN_IFG_2_L
	0.402	0.007214	Amy_Amygdala_L-Aud_HG_L
	0.394	0.008547	MTG_R-Amy_Amygdala_L
	0.394	0.008547	Amy_PHC_L-Vi_Lingual_L
	0.499	0.00085	ASE_MFG_1_L-Amy_Amygdala_R
	0.499	0.00085	ASE_aInsula_R-FN_MFG_1_R
	0.475	0.001514	ASE_MFG_1_L-Aud_HG_R
	0.450	0.00263	ASE_aInsula_R-FN_dMPFC
	-0.434	0.003749	ASE_STG_1_L-FN_SMG_R
	0.426	0.004457	FN_dMPFC-Amy_Amygdala_R
	-0.417	0.005284	dmn_PC-BG_Putamen_L
Visuo-spatial	0.409	0.006247	ASE_MFG_1_L-ASE_aInsula_R
	-0.409	0.006247	SM_SMA_R-BG_Putamen_L
	-0.401	0.007366	dmn_PCC-ASE_STG_1_L
	-0.401	0.007366	ASE_IPL_R-ASE_STG_1_L
	0.401	0.007366	FN_MFG_1_R-Amy_Amygdala_R
	0.393	0.008662	ASE_ACC-ASE_aInsula_R
	0.393	0.008662	ASE_MFG_1_L-Amy_PHC_R
	0.393	0.008662	ASE_STG_2_L-Amy_Amygdala_R

Table.6 List of ROI pairs whose connectivity is correlated with the test-scores with a p<0.01. Positive correlations are green and negative are in red. ROI pairs that occur more than once are in blue. For each test the pairs are arranged in the order of correlation strengths.

DISCUSSION

Technical Challenges

The MNI template is based primarily on Caucasian brains, and there are known differences in sizes of Indian and Caucasian brains and its lobes/structures. As an atlas for the Indian brain is not available, we used the standard MNI template, but manually ensured that each subject image reasonably matched the MNI template after normalization.

Our analysis involves making a large number of comparisons, allowing for Type I errors (i.e. false positives resulting from chance) to creep in. However, due to a small no. of subjects, any rigorous statistical correction for multiple comparisons would lead to Type II errors. So, we have presented the data with uncorrected p values.

Looking through the literature on ICN's, each article reports networks with slightly different nodes, and accordingly, slightly different nomenclatures. While a small number of key nodes remain constant factors across different studies, the rest appear to vary across studies. As we wanted a 'standardized' list of ROI's, we used mostly those from the Allen et. al, 2011 article that reported ROI's based on a large number of (603) subjects.

Overall Comments

Cognitive test scores across multiple domains show several positive correlations among healthy individuals.

All the cognitive tests that showed significant correlations were positively correlated with one another. Thus none of the tests have strong trade-offs with one another as far as performance is concerned. However, some of the connectivity correlates showed trade-offs. E.g. IPL_R and SPL_R to Precentral_R are positively correlated with Bubble - Trail but negatively correlated with EQ. (Note Bubble- Trail and EQ scores show no correlation with one another.

Cognitive Tests

We used clustering analysis to cluster tests into similar groups, and it was reassuring that the resultant clusters did show domain- and hemisphere-wise divisions. Fluency,

Comprehension and Vocabulary – tests of language – always clustered together. 3Back, Stroop, Bubble-Trail and Digit symbol substitution - all tests of executive control and attention – also clustered together. Similarly, right-brain functional domains such as visuospatial ability, eyes test (emotion recognition) and music perception clustered together. Correlations between logical reasoning and mathematics, left and right motor speeds, and melody and rhythm of musical ear test, were only expected.

These clusters show similarity with the Laird et.al., 2011 study, like social cognition i.e. eyes test has a short distance from music, memory is near the language cluster and this is near motor speed which can be classified under the action domain. However there were some surprises, like Empathy Quotient, a social cognitive ability test, clusters with motor speed, while the category test and visuo-spatial test cluster with music tests.

A possible explanation for this discrepancy could be that the clustering as found by Laird et.al., 2011 is based on tasks that are substantially different than ours. Some tests in our battery, like semantic word generation (category fluency), mathematics etc. do not belong to any of the domains mentioned by them.

Hierarchical clustering is sensitive to the method used to calculate the distance matrix and also the method used for clustering. K-means clustering, on the other hand, is sensitive to the choice of initializing centroids and number of iterations.

Clustering using connectivity
We next investigated if subjects could be clustered into groups based on their pattern of performance on our cognitive battery, and if similar groups could be reproduced by clustering based on whole-brain connectivity patterns. So we clustered subjects based on their test scores and separately, based on the connectivity values for the 1540 ROI pairs. The optimal number of clusters were determined using silhouette method in Matlab. This was 4 for the scores dataset, and 8 for the connectivity dataset. Fig. 12 shows how the results of the two clustering methods compare. The y axis depicts the cluster number based on connectivity

clustering while shape indicates the cluster based on scores. The x-axis represents the individual subjects.
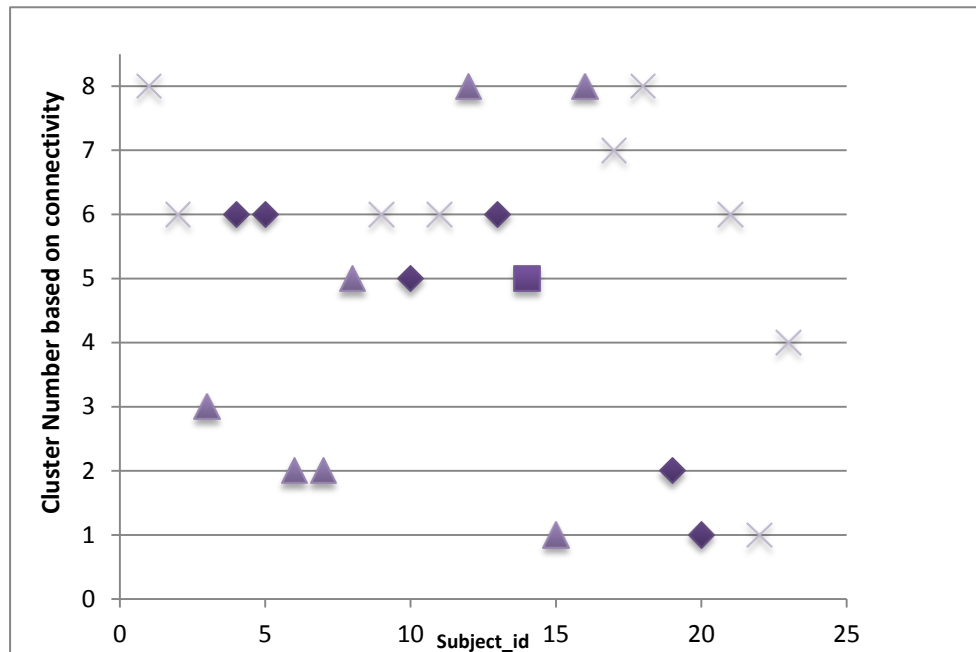

Fig.12 Clustering of subjects is based on connectivity and test scores. Cluster number based on connectivity is on Y-axis. Clustering based on scores is represented by different shapes.

As one can see from the Fig. 12, there is no consistency in the two clustering partitions. As we have tested only a small subset of cognitive abilities subserved by the brain, it is not surprising that overall brain connectivity does not accurately reflect scoring patterns on our battery. For e.g. language is a large domain and involves various different abilities, but we have only tested for comprehension and vocabulary. Similarly, normal visual processing involves a multitude of different tasks, but here we tested only mental rotation tasks.

Network Analysis

Task performance correlates with intra-network connectivity in the TPN and inter-network connectivity between the TPN and TNN, but not with intra-network TNN connectivity.

The most notable conclusion one can make based on the cognitive score-connectivity heat maps (Fig 9-11) is that connectivity between nodes within the task negative network i.e. the DMN, does not appear to be correlated with cognitive

abilities. On the other hand, inter-network, i.e. TPN - TNN connectivity appears relevant to cognitive performance, and several of these ROI pairs are correlated with test scores. Intra- task positive network (TPN - ASE+FN) connectivity appears to be the strongest correlate of task performance, and several of these connections are strongly correlated with cognitive abilities.

Test-wise ROI pair-wise Analysis

Cognitive task performance in healthy individuals is correlated with connectivity between key brain regions known to be involved in performance of that task.

Prior to the testwise discussion of connectivity-cognitive score correlation, I would like to define a "significant node" as any ROI that belongs to an ROI pair whose connectivity is significantly (p-uncorrected<0.01) correlated with a particular test score.

The 3 Back test is a working memory test, and the significant nodes were the Hippocampus, ITG_R and Parahippocampus. fMRI studies have shown that these areas are activated by a visual working memory task like ours (Pessoa et.al.,2002; Glabus et.al., 2003).

The Digit Symbol Substitution (DSS) test is commonly used as a measure of mental speed. ROIs like MFG_L , MFG_R and IFG_L have been shown by task based fMRI studies to be activated during a DSS task (Usui et.al., 2009).. These ROIs are recurring significant nodes in our study as well.

Stroop is a standard test for response inhibition and IFG_L is critical for response inhibition (Swick et.al.,2008) as is STG_R and MFG_L (Liddle et.al.,2001). These are indeed the recurring significant nodes for Stroop task. ITG_R is also another recurring significant node; it has been shown to be involved in word recognition (Nobre et.al.,1994) which is an important part of the Stroop task.

The version of the Trail making test that we used: Bubble Trail - is not only a test of attention, but also a test of response inhibition, visuo-spatial working memory and number processing. IPL and SPL are the most recurring significant nodes for this

test. These areas subserve visuo-spatial working memory, number recognition and processing (Zago et.al.,2002). Putamen_L is another recurring node along with Amygdala_R. The resting state connectivity of the putamen is different in children with attention deficit hyperactivity disorder (ADHD), which as the name suggests, is related to attention deficits (Cao et.al.,2009). The putamen is less connected to STG in ADHD subjects in comparison to controls. Thus our study extends this correlation of the connectivity of the Putamen to STG with attention test scores from pathological conditions to the healthy population. The Amygdala too is known to be involved in attention tasks. (Phelps E. A., 2006).

Logical Reasoning employs frontal areas namely IFG_L, MFG_L along with ACC and PHC according to fMRI studies (Goel et.al.,1998). These were exactly the significant nodes we found for this test. Our logic test involved different types of reasoning tasks. This is probably why we found ITG_R and IFG_R to be significant nodes as well (Parsons et.al.,2001).

Even though the scores in math ability test and logical reasoning were strongly correlated with each other, the ROI pairs whose connectivity was most correlated with math scores were quite different. Some of the significant nodes for the math task are Putamen, IPL, SPL, MFG, Precentral areas etc. The resting state connectivity of the putamen is involved in predicting the ability to acquire arithmetic abilities (Supekar et.al.,2013), and activation of IPL, SPL, MFG, Precentral gyrus has been shown to predict mathematical competence in a task-based fMRI study (Grabner et.al.,2007). The Precuneus is hypothesized to be important in math ability but was not a significant node for us.

The Comprehension task involves word recognition and sentence comprehension. The recurring significant nodes were ITG - which is crucial to word recognition (Nobre et.al., 1994), and STG - crucial to sentence comprehension (Just et.al., 1996). As our task was designed to test memory of reading material, we also found nodes like the Hippocampus, that are important in memory, to be significant. The vocabulary task also involves ITG. It also involves Lingual areas, MFG, MTG etc. that have been shown to be involved in reading in normal children (Gaillard et.al.,2001). Fluency has been correlated with activity in MPFC (Shamay-Tsoory

et.al.,2011) MFG and Lingual areas (Gaillard et.al.,2003), which are the significant nodes. Amygdala_R is also a significant recurring node for us. This area has not been reported to be important to fluency in previous activation studies. However, remembering words is central to the fluency task, and Amygdala is a key region for memory.

Surprisingly, the Hippocampus was not one of the significant nodes we found for the memory test. However, several other areas known to be involved in memory like IFG, Amygdala, (Greenberg et. al., 2005) SPL (Wagner et.al.,2005) and ITG which is involved in word recognition (Nobre et.al.,1994), were the significant nodes we found.

All the types of finger tapping task show activation Precentral, Postcentral, SMA, IPL, IFG_R, Cerebellum etc. and STG might play a role in internal timing of movements (Witt et.al.,2008). Visually paced finger tapping has been shown to involve aInsula. Our motor tapping task allowed the users to see their tapping speed on the screen. The significant nodes for motor tapping task are STG_R and Precentral_R for motor left. Motor_R tapping it is STG_L and Postcentral_L are significant nodes. Note that motor right involves sensorimotor nodes from the left hemisphere while motor left involves those from right hemisphere.

Significant nodes for Empathy quotient are MPFC, Amygdala, Precentral, MFG, IPL and IFG. Precentral areas play a role in emotion recognition (Carr et.al.,2003). Amygdala and IFG are important in empathy (Carr et.al.,2003). MFG plays a role in Theory of Mind tasks (Goel et.al.,1995). Emotional processing takes place in dorsal MPFC (Northoff et.al.,2004). As aInsula is also known to play a crucial role in empathy we had expected it to be a significant node but we did not find it to be. IPL has been shown to have mirror neurons along with IFG that a play vital role in empathy.

Category task is semantic word generation test. SMA, aInsula, Precentral and MFG are significant nodes in our task and are also known to be associated with word production (Alario et.al.,2006). Putamen also underlies word generation (Klein et.al.,1995). Precuneus is important for memory retrieval (Lundstrom et.al.,2005).

The MET task had two parts: melody and rhythm discrimination. Though these are correlated with each other and similar in some ways they are also significantly different. The significant nodes for melody discrimination task were MFG, Precuneus and MPFC. MFG and Precuneus are known to play a role in melody task (Spada et.al., 2014). PHC is another significant node, probably because of the memory component of the test. MPFC is a central node that plays a role in musicality and also memory (Janata P., 2009). It is also an important significant node for rhythm discrimination task. Auditory area (HG) was a significant node only for Rhythm task and not melody one for us. We have no explanation for this discrepancy. PHC and Hippocampus were also significant nodes for the rhythm task probably because of the memory component of the test.

The Eyes Test was a test of emotion recognition and the significant nodes for this test namely Amygdala and MPFC - are crucial to emotion recognition (Phan et.al.,2002). The Calcarine and Lingual gyrus are also significant nodes. The test heavily relies on visual stimulus processing. These areas have been shown to be involved in visual emotion recognition like our test (Adolphs R., 2002).

The Visuo-spatial test assessed the subject's ability for mental rotation. The significant nodes are STG, Amygdala, MFG, IPL, and aInsula. STG, IPL, MFG have been shown to be involved in mental rotation (Alivisatos et. al.,1997) while the Amygdala plays a role in visuo-spatial memory (Pegna et.al., 2002). IPL, aInsula, ACC are some of the significant nodes that are consistently reported in several mental rotation studies (Zacks. J.,2008). Putamen another significant node is known to be involved in hand rotation task (Bonda et.al.,1995).

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