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Cognitive Neuroscience Neuroimaging Repository for the Adult Lifespan

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Abstract

With recent advances in neuroimaging technology, it is now possible to image human brain function *in vivo*, which revolutionized the cognitive neuroscience field. However, like any other newly developed techniques, the acquisition of neuroimaging data is costly and logistically challenging. Furthermore studying human cognition requires acquiring a large amount of neuroimaging data, which might not be feasible to do by every researcher in the field. Here, we describe efforts in our group to acquire one of the largest neuroimaging datasets that aims to investigate neural substrates of age-related cognitive decline, which will be made available to share with other investigators. Our neuroimaging repository includes up to 14 different functional images for more than 486 subjects across the entire adult lifespan in addition to their 3 structural images. Currently, data from 234 participants have been acquired, including all the 14 functional and 3 structural images which is planned to be increased to 375 participants in the next few years. A complete battery of neuropsychological tests was also administered to all participants. The neuroimaging and the accompanying psychometric data will be available through an on-line and easy to use data sharing website.

Introduction

Investigating the neuronal underpinnings of cognitive decline in normal aging with neuroimaging requires sampling the entire adult lifespan with many different imaging modalities. Imaging cognition is an active area of research and a challenging task. One possibility is to image the brain while performing a few tasks targeting the same cognitive domain. A direct consequence of such approaches is the need for a large collection of the images on a single subject, which is not only costly but also logistically difficult. The Cognitive Neuroscience Neuroimaging Repository (CNR) contains cross-sectional neuroimaging data from past and on-going projects in the Cognitive Neuroscience Division of Neurology Department and Taub Institute at Columbia University. It contains fMRI data from 14 different cognitive tasks targeting four cognitive domains (vocabulary, perceptual-speed, fluid reasoning, and memory). Even though fMRI is the dominant modality in these

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studies, other modalities are also collected to provide valuable information. Thus, CNR includes MPRAGE, DTI, and FLAIR images as part of the structural image acquisition. CNR also includes resting-state continuous ASL, and resting-state fMRI as the baseline functional neuroimaging data. In addition 14 well-known cognitive tasks representing distinct cognitive domains have been modified and computerized to be executable during scan acquisition. Block, event-related, and mixed designs are all used for implementing these tasks.

Participants in this repository are sampled from six decades of the adulthood life span (from 20 to 80 years) while controlling for many known confounding factors including but not limited to: education, handedness, medical/psychiatric conditions/medications, native-speaking English, and area of residence. Currently, there are more than 635 participants in our studies with 486 having at least some neuroimaging data and 234 with a completed neuroimaging data set. The goal is to have at least 50 participants in the first three decades and 75 in the last three decades, resulting in complete data on 375 participants (meaning to have at least 3 fMRI scans in each of the four cognitive domains). Table I summarizes the current number of images for each fMRI task and the rest of the modalities.

In addition to neuroimaging data, a complete battery of neuropsychological tests has been administered to all participants. The neuropsychological data are also stored in the same repository, which will be linked to neuroimaging data through our new Collaborative Informatics and Neuroimaging Suite (COINS) database. We are currently in the process of migrating our data to COINS, which will make storing, retrieving, mining, and sharing convenient.

To study the normal aging brain in contrast to pathological aging a subset of the participants in the last two decades (n~100) has received PET scanning for fibrillar forms of beta amyloid with ¹⁸F-Florbetaben.

Scanners and Acquisition Parameters

All MRI scans in CNR are acquired with the same 3.0 Tesla Achieva Magnet Philips scanner (software R2.6.3.6) with functional MRI, ASL, and DTI options. Table II summarizes acquisition parameters for each of the MRI modalities acquired in this database. Studies acquiring data from multiple scanners are often limited because scanners themselves account for a majority of variance in the data (Biswal et al., 2010). Using a single scanner has the benefit of controlling for this confounding factor.

PET images were acquired over a period of 20 minutes in 4×5 minute frames on an MCT PET/CT scanner (Siemens) in dynamic, 3D imaging mode beginning 50 min after injection of ¹⁸F-Florbetaben. Transmission scans were done prior to the scan. An accompanying structural CT scan (in-plane resolution = 0.58×0.58 mm, slice thickness = 3mm, field of view (FOV) = 296×296 mm, number of slice = 75) was also acquired in the same machine at the same time of the PET scan.

Recruitment and Participants

Participants were recruited through random market-mailing within 10 miles of the Columbia University Medical Center. This recruitment approach is intended to obviate cohort effects that might be present by using convenience samples. All subjects are compensated for participation. Informed consent is obtained prior to testing, with approval from the Columbia University Medical Center Institutional Review Board. All subjects were required to be native English speakers, strongly right-handed, and have at least a fourth grade reading level. Subjects were screened for MRI contraindications and hearing or visual impairment that would impede testing. Subjects are free of medical or psychiatric conditions that could affect cognition. Careful screening ensured that the older subjects did not meet criteria for dementia or Mild Cognitive Impairment (MCI). A score greater than 130 was required on the Mattis Dementia Rating Scale (Mattis, 1988). Further, performance was required to be within age-adjusted normal limits (one and a half standard deviation below each age-decade median word recall) on a list-learning test (SRT;(Buschke and Fuld, 1974)), and participants were required to have no or minimal complaints on a functional impairment questionnaire (Blessed et al., 1968). A neuroradiologist reviews each subject's T1 scan and confirms that there are no clinically significant findings for any of the subjects. Any significant findings are conveyed to the participant's primary-care physician. However, no clinically significant findings were identified or removed.

Psychometric Measurements

Every participant enrolled in the study is administered the same neuropsychological battery; the Mattis Dementia Rating Scale (Mattis, 1988), WAIS-III Letter-Number Sequencing (Wechsler, 1997), American National Adult Reading Test (Grober & Sliwinski, 1991), Selective Reminding Test immediate recall (SRT;(Buschke and Fuld, 1974)), WAIS-III Matrix Reasoning (Wechsler, 1997), SRT delayed recall and delayed recognition (Buschke and Fuld, 1974), WAIS-III Digit-Symbol (Wechsler, 1997), Trail-Making Test (Reitan, 1958), Controlled Word Association (C-F-L) and Category Fluency (animals) (Benton & Hampshire, 1976), Stroop (Golden, 1975), Wechsler Test of Adult Reading (Wechsler, 2001), WAIS-III Vocabulary (Wechsler, 1997), WAIS-III Block Design (Wechsler, 1997), and Wisconsin Card Sorting Test (Grant & Berg, 1993).

Each participant is also given a packet of questionnaires to complete. The packet includes the Blessed Functional Activities Scale (Blessed et al, 1968), the International Personality Item Pool (Goldberg, 1999), as well as several questionnaires developed in-house: an occupational survey, two exercise questionnaires, a leisure activities questionnaire, a sociodemographic questionnaire, an education questionnaire, and a risk factor survey.

A subset of participants also underwent evaluation with portions of the NIH EXAMINER battery to assess executive function (Kramer et al, 2014). Tasks administered from this study include the Flankers task, the Continuous Performance Task, the Anti-saccades task, and the Set Shifting task. 246 participants have currently undergone this battery.

fMRI tasks and designs

In total, there are fMRI data for 14 different cognitive tasks in addition to resting state data. 12 tasks are intended to represent four latent cognitive abilities: vocabulary, perceptual-speed, fluid reasoning, memory. Two additional tasks tap working memory and executive control.

Three vocabulary and three perceptual-speed tasks have been implemented with a similar structure. Figure 1 shows the timing of these block design tasks along with a table representing the parameters of each task in this design. Snapshots of each task is also provided in this figure. All six tasks have 36 seconds of initial fixation (IF) and 28 seconds of inter-block fixation (IBF).

The vocabulary tests are: 1) *Synonyms*: subjects match a given word to the word most similar in meaning. The probe word is presented in all capital letters at the top of the screen, and four numbered choices are presented below. 2) *Antonyms*: participants match a given word to the word most different in meaning. The probe word is presented in all capital letters at the top of the screen, and four numbered choices are presented below. 3) *Picture Naming*: subjects verbally name pictures. Target pictures consisted of 40 colored bitmap images, adapted from the picture naming task of the WJ-R Psycho-Educational battery (Woodcock et al, 1989).

The perceptual speed tasks are: 1) *Digit Symbol*: this task uses a code table to associate symbols with digits. The code table is presented on the top of the screen, consisting of numbers one through nine, each paired with an associated symbol. Below the code table an individual number/symbol pair is presented. Subjects are asked to indicate whether the individual pair is the same as that in the code table using a differential button press. 2) *Letter Comparison*: In this task, two strings of letters, each consisting of three to five letters, are presented alongside one another. Subjects indicate whether the strings are the same or different using a differential button press. 3) *Pattern Comparison*: In this task, two figures consisting of varying numbers of lines connecting at different angles are presented alongside one another. Subjects indicate whether the figures are the same or different using a differential button press.

Figure 2 illustrates the timing and trials of three fluid reasoning tasks along with specific parameters used for each one. 1) *Paper Folding*: participants select the pattern of holes that would result from a sequence of folds and a punch through the folded paper. The folding sequence is given on the top of the screen, and five unfolded options are given underneath in one row. 2) *Matrix Reasoning*: subjects select which pattern best completes the missing cell in a matrix. Subjects are given a matrix that is divided into nine cells, in which the figure in the bottom-right cell is missing. Below the matrix, they are given eight figure choices, and they are instructed to evaluate which of the figures would best complete the missing cell. 3) *Letter Sets*: subjects select which of five groups of letters is different from the others. Subjects are presented with five sets of letters, where four out of the five sets have a common rule (e.g. have no vowels), with one of the sets not following this rule. Subjects are instructed to select the unique set.

Three episodic memory tasks, one working memory tasks and one set-switching task are implemented as mixed design. The timing and parameters of these tasks along with a snapshot of their instruction and probe question are given in Figure 3. The episodic memory tasks are: 1) *Logical memory*: this task measures the number of details recognized across two stories. Subjects are required to remember specific details from stories presented on the computer screen, then asked to answer detailed multiple-choice questions about the story, with four possible answer choices. 2) *Word order recognition*: a list of twelve words is presented one at a time on the screen, and subjects are instructed to remember the order in which the words are presented. Following the word list they are given a probe word at the top of the screen, and four additional word choices below. They are instructed to choose the word that immediately followed the word given above. 3) *Paired associates*: subjects are supposed to recognize the second words from word pairs. Six pairs of words are presented, one at a time, in the instruction phase, and subjects are instructed to remember the pairs. Following the pairs, they are given a probe word at the top of the screen and four additional word choices below.

The working memory test is *Letter Sternberg*. Subjects view a set of uppercase letters (of 1, 3 or 6 items) for 3 seconds, and are asked to memorize them during an extended delayed-retention phase. Then a probe lowercase letter is presented during a retrieval phase and subjects indicate whether or not the presented probe letter was in the previously viewed set of uppercase letters.

The set-switching task is *Executive Control Function*: subjects view a single letter in the center of the screen and are asked to distinguish whether the letter is upper/lower case or it is vowel/consonant. The required task is indicated by color of the letters. An instruction provided in the beginning of each block describes the task for that block. In total there are three instruction types, two single and one set-switch instructions. In the single instruction blocks subjects are simply required to decide whether the presented letter is upper/lower case or vowel/consonant, with red letters associated with the former task and green with the latter task. In the single task blocks all letters are of the same color and the task remains constant throughout the block. In the dual task blocks letters appear in both colors, requiring subjects to switch between the two tasks. All tasks blocks also contain white letters, indicating a no-go trial. (More details of this task are provided in Koechlin et al, 2003).

Letter Sternberg and Executive Control Function tasks were implemented and computerized in PsyScope (Cohen et al, 1993), and the rest of the tasks are implemented and computerized in E-Prime (Schneider et al, 2012).

Pre-Processing and Data Analysis

Each subject's structural T1 scan was reconstructed using the FreeSurfer v.5.1 software package (<http://surfer.nmr.mgh.harvard.edu/>), which segments both cortical and subcortical regions based on the morphology of the gyri and sulci in each individual participant. Each subject's white and gray matter boundaries as well as gray matter and CSF boundaries were visually inspected slice by slice by a single trained/experienced technician. Manual control points were added in the case of any visible discrepancy, and reconstruction was repeated

until satisfactory results were reached for every subject (Fjell et al., 2009). Second level quality assurance is done by separate expert by overlaying the borders of the segmented cortical, and subcortical regions on top of the original image to minimize/eliminate any inaccuracy in the segmentation process.

We analyzed FLAIR images for white matter hyper-intensities using in-house software (Brickman et al., 2011) and manually inspected by a designated and trained technician. The quantified white matter hyper-intensity volumes were stored and we did not exclude subjects based on their volumes.

DTI data have been analyzed using FSL (FMRIB's Software Library v. 5.0.7) and FreeSurfer through a processing stream called TRACULA (Tracts Constrained by Underlying Anatomy) distributed as part of the FreeSurfer v. 5.2 library (Yendiki, et al., 2011). FMRIB's Diffusion Toolbox (FMRIB's Software Library v. 4.1.5) standard DTI processing steps including eddy current correction, tensor estimation, and bedpost is used to prepare the data for TRACULA.

ASL data have been processed using SPM8. For each voxel, computation of CBF was weighted by the tissue-type posterior probability. To remove any signal from scalp and non-brain tissue, a mask including only voxels with an SE-EPI intensity > 0.80 was obtained and used to yield an average CBF image for each subject before any statistical analysis. For the voxelwise analysis (in both multi- and univariate versions), CBF images were spatially smoothed with a 6 mm kernel. No smoothing was carried out for the ROI analysis.

All fMRI images were pre-processed and statistically analyzed using the FSL standard pre-processing pipeline. Images were visually inspected for imaging artifacts, neurological pathology and excessive head motion. All volumes in the fMRI data are spatially aligned/registered to the middle volume using rigid-body transformation. The timing of each slice's time-series were temporally adjusted to the middle slice sampling time using *Sinc* interpolation. Spatial smoothing with 5 mm³ non-linear kernel has been applied to all volumes data. Intensity normalization was carried out such that the 50th percentile of all volumes intensities after removing the background noise was 10^4 for every subject. The time-series were then high-pass filtered using a Gaussian filter with cut-off frequency of 0.008 Hz. For analysis in standard space, spatial normalization was performed by combining two transformations obtained from 1) nonlinear registration of the accompanying T1 image to MNI152 template and 2) intermodal rigid-body co-registration of each subject's mean volume and T1 image. Autocorrelations within the time-series were corrected for by pre-whitening the data. Resting-state fMRI images were also analyzed in the subjects' native space using in-house developed software package (Razlighi et al., 2014).

De-identification, Database, and Sharing

Once the responding volunteer passed the initial phone screening and scheduled for the first on-site appointment a subject ID is assigned to him/her. This subject ID also indicates for which study the subject is recruited. Once the subject ID is assigned, there was no use of subject name or any other identification type (e.g. birth date, social security number, etc.) in

any of the clinical assessments, questionnaires, psychometric data, or neuroimaging data. The subject identifier key was the only link between subject ID and identifying information. This subject identifier key is encrypted and only accessible with IRB-approved personnel and it is only used for contacting the participants in the future.

Currently all imaging data were pushed into our DICOM server by the scanner and then transferred to our 120TB RAID storage and converted to NIFTI format. We are in the process of migrating our in-house built database to COINS) database. COINS is web-based neuroimaging and neuropsychology database software suite that offers flexible, automatable data upload/import/entry options, fast and secure sharing of data among researchers, querying and exporting of data, real-time reporting, and HIPAA and IRB compliant study-management tools suitable to large institutions as well as smaller scale researchers (Scott et al, 2011). Using this database we are hoping to increase the reliability and accessibility of our data. We also aim to build a stronger relation between psychometric data and neuroimaging data. Once the migration is completed we should be in a position to share our data through an on-line and easy to use database system provided by COINS.

Conclusion

We are in the process of building a large, comprehensive cross-sectional database that includes comprehensive neuroimaging and behavioral data for adults across the adult lifespan. Our efforts to harmonize data acquisition and data analysis procedures together with our newly-implemented web-based databasing system will facilitate collaboration with other investigators who are interested in age-related cognitive differences. We hope that our efforts result in a valuable resource for the field.

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Highlights

1. A comprehensive cross-sectional cognitive aging neuroimaging repository is presented.
2. The number of participants in each fMRI scans (14 different cognitive tasks) are listed along with structural and baseline fMRI and ASL.
3. The complete neuropsychological battery, which was administered on all subjects are listed.
4. Each fMRI data design and the defaults processing stream is explained briefly.
5. The plan for sharing through an easy to use on-line database is explained.

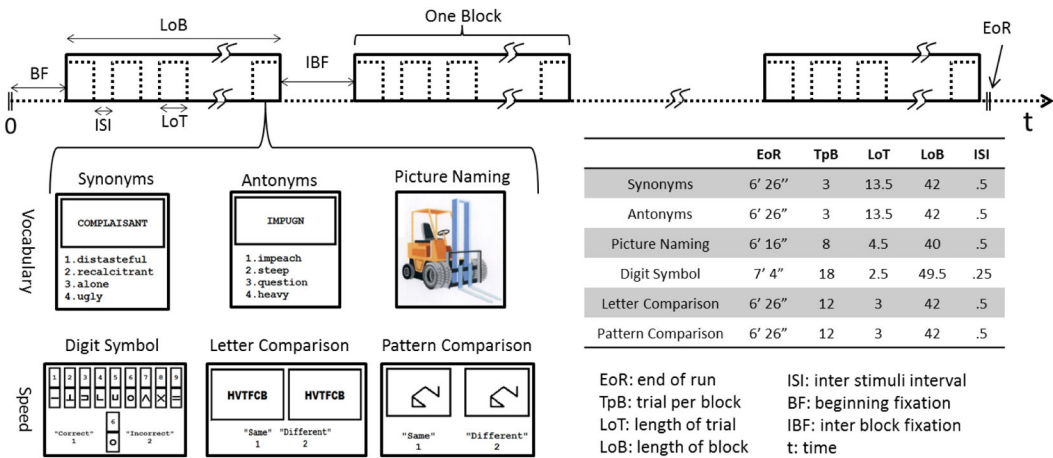


Figure 1.
Timing, snapshot, and parameters of the six vocabulary and speed tasks

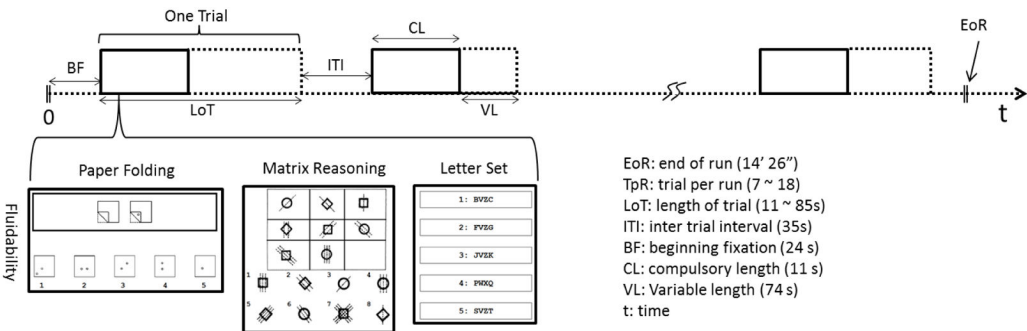


Figure 2.
Timing, snapshot, and parameters of the three fluid ability tasks

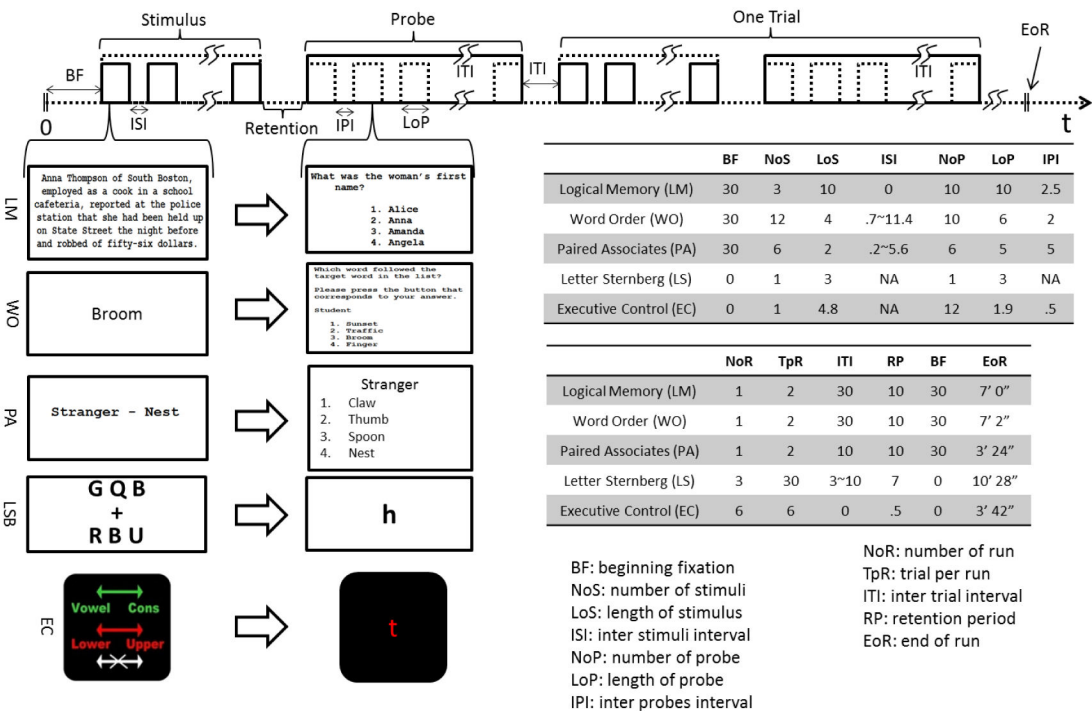


Figure 3. Timing, snapshot, and parameters of the three memory tasks, letter Sternberg, and executive context tasks

Table I

Demographic of the participants in CNR

Image Modality/Task	Age Range															Total		
	20-30			30-40			40-50			50-60			60-70					70-80
	#Subjects (Female%)	Education Mean±Std	#Subjects (Female%)	Education Mean±Std	#Subjects (Female%)	Education Mean±Std	#Subjects (Female%)	Education Mean±Std	#Subjects (Female%)	Education Mean±Std	#Subjects (Female%)	Education Mean±Std	#Subjects (Female%)	Education Mean±Std	#Subjects (Female%)	Education Mean±Std	# Subjects (Female%)	Education Mean±Std
T1	115 (63%)	15.63±1.97	63 (67%)	16.37±2.52	41 (46%)	15.73±2.62	56 (50%)	15.77±2.21	123 (52%)	16.05±2.68	51 (57%)	17.37±2.54	449 (57%)	17.37±2.54	51 (57%)	17.37±2.54	449 (57%)	16.07±2.47
FLAIR	105 (63%)	15.64±2.05	59 (66%)	16.31±2.48	42 (45%)	15.76±2.6	52 (50%)	15.75±2.23	120 (52%)	16.08±2.68	49 (55%)	17.49±2.5	427 (56%)	17.49±2.5	49 (55%)	17.49±2.5	427 (56%)	16.1±2.49
DTI	103 (62%)	15.65±2.05	60 (68%)	16.37±2.5	42 (45%)	15.76±2.6	48 (50%)	15.9±2.13	118 (51%)	16.11±2.67	48 (54%)	17.44±2.5	419 (56%)	17.44±2.5	48 (54%)	17.44±2.5	419 (56%)	16.13±2.48
ASL	107 (63%)	15.59±1.99	61 (67%)	16.37±2.48	42 (45%)	15.76±2.6	53 (51%)	15.79±2.23	118 (53%)	16.07±2.69	49 (55%)	17.49±2.5	430 (57%)	17.49±2.5	49 (55%)	17.49±2.5	430 (57%)	16.09±2.48
Resting State fMRI	106 (62%)	15.64±2.04	61 (67%)	16.37±2.48	42 (45%)	15.76±2.6	52 (50%)	15.75±2.23	119 (51%)	16.08±2.69	49 (55%)	17.49±2.5	429 (56%)	17.49±2.5	49 (55%)	17.49±2.5	429 (56%)	16.1±2.49
Antonym	58 (64%)	15.64±2.01	56 (66%)	16.3±2.52	41 (46%)	15.73±2.62	52 (50%)	15.71±2.17	46 (46%)	16.13±28	46 (52%)	17.54±2.42	299 (55%)	17.54±2.42	46 (52%)	17.54±2.42	299 (55%)	16.16±2.5
Synonym	59 (63%)	15.64±1.99	56 (66%)	16.3±2.52	40 (47%)	15.68±2.63	52 (50%)	15.71±2.17	45 (47%)	16.09±2.82	46 (52%)	17.54±2.42	298 (55%)	17.54±2.42	46 (52%)	17.54±2.42	298 (55%)	16.15±2.5
Picture Naming	58 (64%)	15.64±2.01	56 (66%)	16.3±2.52	41 (46%)	15.73±2.62	51 (49%)	15.67±2.17	45 (44%)	16.23±2.76	45 (53%)	17.62±2.39	296 (55%)	17.62±2.39	45 (53%)	17.62±2.39	296 (55%)	16.18±2.5
Digit Symbol	59 (63%)	15.64±1.99	56 (66%)	16.3±2.52	41 (46%)	15.73±2.62	52 (50%)	15.71±2.17	46 (46%)	16.13±2.8	46 (52%)	17.54±2.42	300 (55%)	17.54±2.42	46 (52%)	17.54±2.42	300 (55%)	16.16±2.5
Letter Comparison	58 (64%)	15.64±2.01	56 (66%)	16.3±2.52	41 (46%)	15.73±2.62	51 (49%)	15.67±2.17	46 (46%)	16.13±2.8	46 (52%)	17.54±2.42	298 (55%)	17.54±2.42	46 (52%)	17.54±2.42	298 (55%)	16.16±2.51
Pattern Comparison	58 (64%)	15.64±2.01	56 (66%)	16.3±2.52	41 (46%)	15.73±2.62	51 (49%)	15.67±2.17	45 (44%)	16.23±2.76	46 (52%)	17.54±2.42	297 (55%)	17.54±2.42	46 (52%)	17.54±2.42	297 (55%)	16.17±2.5
Paper Folding	61 (64%)	15.71±2.03	56 (64%)	16.32±2.61	40 (45%)	15.9±2.58	52 (48%)	15.79±2.1	51 (45%)	16.33±2.64	48 (52%)	17.4±2.47	308 (54%)	17.4±2.47	48 (52%)	17.4±2.47	308 (54%)	16.23±2.47
Matrix Reasoning	62 (65%)	15.72±2.01	56 (64%)	16.32±2.61	40 (45%)	15.9±2.58	52 (48%)	15.79±2.1	50 (44%)	16.36±2.66	48 (52%)	1748±2.39	308 (54%)	1748±2.39	48 (52%)	1748±2.39	308 (54%)	16.24±2.46
Letter Set	61 (64%)	15.71±2.03	56 (64%)	16.32±2.61	40 (45%)	15.9±2.58	52 (48%)	15.79±2.1	50 (44%)	16.36±2.66	48 (52%)	17.48±2.39	307 (54%)	17.48±2.39	48 (52%)	17.48±2.39	307 (54%)	16.25±2.46
Logical Memory	61 (64%)	15.71±2.03	56 (64%)	16.32±2.61	40 (45%)	15.9±2.58	52 (48%)	15.79±2.1	50 (44%)	16.36±2.66	49 (53%)	17.3±12.45	308 (54%)	17.3±12.45	49 (53%)	17.3±12.45	308 (54%)	16.23±2.47
Word Order	61 (64%)	15.71±2.03	56 (64%)	16.32±2.61	40 (45%)	15.9±2.58	52 (48%)	15.79±2.1	50 (44%)	16.36±2.66	48 (52%)	17.48±2.39	307 (54%)	17.48±2.39	48 (52%)	17.48±2.39	307 (54%)	16.25±2.46
Paired Associates	61 (64%)	15.71±2.03	56 (64%)	16.32±2.61	40 (45%)	15.9±2.58	52 (48%)	15.79±2.1	49 (45%)	16.32±2.67	48 (52%)	17.48±2.39	306 (54%)	17.48±2.39	48 (52%)	17.48±2.39	306 (54%)	16.24±2.46
Letter Sternberg	54 (67%)	15.54±1.95	7 (86%)	17±1.41	0	NA	2 (50%)	18±2	86 (57%)	16.34±2.71	5 (80%)	17±2.68	154 (62%)	17±2.68	5 (80%)	17±2.68	154 (62%)	16.13±2.46
Executive Control	71 (65%)	15.51±1.94	7 (86%)	17±1.41	0	NA	2 (50%)	18±2	104 (54%)	16.07±2.68	5 (80%)	17±2.63	189 (60%)	17±2.63	5 (80%)	17±2.63	189 (60%)	15.94±2.42

Table II

Acquisition parameters for all image modalities in CNR

Sequences	TE/TR (ms)	flip Angle (deg)	In-plane Resolution	Voxel Size (mm)	Acquisition time	Slice Thickness/gap (mm)	Slices
EPI	20/2000	72	112×112	2×2×3	Task Depend	3/0.0	41
MPRAGE	3/6.5	8	256×256	1×1×1	~4' 55"	1/0.0	180
FLAIR	125/11000	90	256×192	1×1×5	4' 24"	4/0.5	30
DTI (55 dir)	69/11032	90	112×112	2×2×2	12' 56"	2/0.0	75
ASL	30/5000	90	64×64	3.5×3.5×6.5	~4' 30"	7.5/1.5	15