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Association of brain network efficiency with aging, depression, and cognition

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Abstract

Objectives—Newly developed techniques for understanding brain connectivity have emerged with the application of graph theory-based measures to neuroimaging modalities. However, the cognitive correlates of these measures, particularly in the context of clinical diagnoses like major depression, are still poorly understood. The purpose of this study was to compare four measures of network efficiency derived from novel techniques for understanding white matter connectivity on their associations with aging, depression, and cognition.

Design—Cross-sectional neuroimaging study

Setting—General community

Participants—We recruited 43 healthy comparison subjects and 40 subjects with major depressive disorder who volunteered in response to advertisements.

Measurements—Brain network efficiency measures were generated from diffusion tensor imaging-derived structural connectivity matrices using the Brain Connectivity Toolbox (www.brain-connectivity-toolbox.net). Information processing speed and decision making were assessed with the Trail Making Test and the Object Alternation task, respectively.

Results—All four network efficiency measures correlated negatively with age. In the depressed group, normalized global efficiency was negatively correlated with depression severity while increasing global efficiency was associated with poorer performance on Object Alternation.

Conclusions—Brain network efficiency measures may represent different aspects of underlying network organization depending on the population and behaviors in question.

Objective

Diffusion tensor imaging (DTI) has emerged as a popular way to explore white matter integrity in healthy as well as disease populations. With DTI, white matter tracts can be constructed and virtually dissected to analyze individual differences in structural connectivity. One of the novel ways that DTI tractography has been used recently is in the application of graph theory-based network analysis. In brief, graph theory-based network analysis models ‘the brain as graph’ characterized by nodes (i.e., brain regions) and edges (i.e., functional or structural connections between regions) that connect nodes. Once the

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brain has been modeled in this manner, various network metrics can be calculated that elucidate the function and organization of the brain as a network (22). For instance, studies using this technique have detected differences in disease populations in the organization of the brain in terms of modules or communities thought to reflect pathological brain changes associated with the disease (9,24). A frequently used measure associated with this technique is network efficiency, a measure of network integration. Network efficiency represents the number of steps required to get information from one part of the derived brain network to another. It is thought that highly efficient networks require very few steps or shorter path lengths, while inefficient networks require multiple steps. There are two ways networks can increase their efficiency, integration and randomization. With network integration, distributed information is easily combined throughout a network with strategically placed connections (22). With network randomization, an increase in randomly placed connections can reduce the path length and thus increase network efficiency.

Network efficiency can be measured using a number of different neuroimaging modalities. Structural brain networks are often created using data from DTI or the structural covariance of gray matter volumes. Functional brain networks can be generated from resting-state functional magnetic resonance imaging (rs-fMRI). One of the first studies to examine the association of age with this concept of network efficiency published by Achard and Bullmore demonstrated reduced efficiency in older adults using rs-fMRI (1). Contrary to this result, using DTI-derived networks, Gong et al demonstrated that global efficiency as a function of network cost (integrated global efficiency) did not decline with age (10). However, a study by Wen et al utilizing similar DTI-based methods confirmed earlier findings by Achard and Bullmore that global network efficiency declines with age (26). Further complicating the picture, in a study looking at gray matter structural covariance networks in three age groups, younger subjects (14–40 years) had lower global efficiencies compared to older subjects (61–80 years) (27).

There are similarly conflicting reports demonstrating alterations in global efficiency in various disease states including depression. In our own recent study using gray matter structural covariance, we found untreated late-life depressed subjects had significant lower global efficiencies compared to healthy elderly subjects (2). Using rs-fMRI to generate functional connectivity graphs, global efficiency was reported to be significantly *higher* in younger first-episode, depressed subjects compared to healthy comparison subjects (29). In contrast, using DTI-generated networks, it has been shown that global efficiency was reduced in population of remitted geriatric depression subjects compared to healthy elderly control subjects (3). These differences could be due to MRI modalities employed in graph theory analyses and/or the populations evaluated; however, more work needs to be done exploring the types of network efficiency available for interrogation and their associations to study-specific populations in question.

In addition to disease states, studies have revealed that brain network efficiency is associated with aspects of cognitive function in both healthy and clinical populations. Initial studies demonstrated that IQ was positively associated with global efficiency in healthy adults (17,25). Older healthy adults demonstrated that both local and global efficiency (measures of network segregation and network integration, respectively) were positively associated with a composite index of executive function and information processing speed (26). In a study of mild cognitive impairment, Shu and colleagues demonstrated that global efficiency was positively correlated with information processing speed (23). Similar findings have recently been reported in type 2 diabetes (21). Little to no work associating network efficiency metrics and cognition in depression has been reported despite the relatively well-established link between executive function and information processing speed in this population.

While the aforementioned studies have examined altered network efficiency associated with aging, depression across the lifespan, and cognition, it is not clear whether increased network efficiency more closely reflects network integration (as suggested by aging studies) or network randomization (implied by the functional studies of major depression). The purpose of this study was to conceptually evaluate four different measures of network efficiency derived from white matter connectivity analyses on their associations with aging, depression, and cognition. We examined three measures of global efficiency and local efficiency previously documented in the literature and compared a depressed versus never depressed sample ranging from age 30 to 88, on measures of information processing speed and decision making. We hypothesized that if efficiency reflects network integration, then brain network efficiency would be negatively associated with age and depression severity and positively associated with information processing speed and executive function.

Methods

Subject Recruitment

We recruited 40 subjects with major depression and 43 healthy comparison subjects from the greater Chicago area through flyers and local advertisements as part of a larger ongoing neuroimaging study at the University of Illinois at Chicago (UIC). The inclusion criteria for all subjects were 30 years of age and older, medication-naïve or anti-depressant free for at least two weeks (in the case of our depressed subjects) and no history of unstable cardiac or neurological diseases. The exclusion criteria included: schizophrenia, bipolar or any psychotic disorders; history of anxiety disorder outside of major depressive episodes; history of head trauma; history of substance abuse; contraindications to MRI such as metal implants. This study was approved by the University of Illinois-Chicago Institutional Review Board, and written informed consent was obtained from each participant.

All eligible subjects were assessed by a trained research assistant with the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). The severity of depression was quantified by a board-certified/board-eligible psychiatrist (AK or OA) using the 17-item Hamilton Depression Rating Scale (11). At the time of enrollment, depressed subjects met DSM-IV criteria for MDD and required a score of 15 or greater on the HAM-D. Subjects were also administered the Center for Epidemiologic Studies of Depression (CES-D) scale as an independent measure of depression severity (20). The CES-D was used for correlation analyses as the HAM-D was the measure used in the determination of subject eligibility for depression.

MRI Image Acquisition

All brain MRI data were acquired using a Philips Achieva 3T scanner (Philips Medical Systems, Best, the Netherlands) with 8-element SENSE (Sensitivity Encoding) head-coil. Subjects were fitted with soft ear plugs, positioned comfortably in the coil, and instructed to remain still. Foam pads were used to minimize head motion. For each subject, DTI images were acquired using single-shot spin-echo echo-planar imaging (EPI) sequence (field of view or FOV=240mm; acquired voxel size = 2.21×2.21×2.20mm; reconstructed voxel size = 0.83×0.83×2.2mm; TR/TE=6,994/71ms; Flip angle=90°). Sixty seven contiguous axial slices aligned to the anterior commissure–posterior commissure (AC-PC) line were collected along 32 gradient directions with $b=700\text{s/mm}^2$ and one minimally diffusion-weighted scan (the b_0 image). Parallel imaging was utilized with p-factor of 2.5 to reduce scan time to approximately 4 minutes.

Network Analysis

To generate brain network data, a pipeline was constructed which integrates multiple image analysis technique based on previously published methods (14,23). Diffusion weighted images were eddy current corrected using the automatic image registration tool in DTI-Studio (<http://www.mristudio.org>;12) by registering all diffusion-weighted images to their corresponding b_0 images. Two eddy current correction (ECC) techniques were employed: rigid body (rotation and translation, 6 parameters) and affine (rotation, translation, scaling and shear, 12 parameters). This was followed by the computation of diffusion tensors then deterministic tractography using the Fiber Assignment by Continuous Tracking (FACT) algorithm built into the DTI-Studio program. For each subject, tractography was first performed by tracking the whole brain, initiating tracts at each voxel. Fiber tracking was stopped when FA value falls below 0.15 or a turning angle becomes larger than 60° .

T1-weighted images were used to generate label maps using the FreeSurfer image analysis suite (<http://surfer.nmr.mgh.harvard.edu/>) for volumetric segmentation (6–8). Each label map is composed of 87 different gray matter regions of interest (ROIs), which include cortical and subcortical regions as well as the brainstem and cerebellum.

Brain structural networks were generated by counting the number of reconstructed streamlines from the white matter tractography data connecting every pair of gray matter ROIs (i.e. the “nodes”) defined by FreeSurfer’s parcellation atlas. The resulting matrices were then analyzed using a set of Matlab-based functions implemented in the Brain Connectivity Toolbox (<http://brain-connectivity-toolbox.net/>) to generate our measures of global and local network efficiency (22). Three measures of global network efficiency were obtained. Native global efficiency (E_{native}) was calculated as the global efficiency of the actual network with no thresholding. Normalized global efficiency (E_{norm}) was the ratio of the E_{native} to the global efficiency of a random network of equal size and cost to the actual network. Integrated global efficiency (E_{int}) measured global efficiency as a function of cost. Network cost was calculated as the number of edges in the network as a fraction of all possible edges in the network. Local efficiency (E_{loc}) is the efficiency of a subnetwork containing a particular node and its network neighbors. Table 1 outlines these metrics in greater detail.

Neuropsychological Battery

In addition to neuroimaging, subjects completed a comprehensive neuropsychological protocol. Of relevance to the present study were measures of executive function and information processing with timed components. To this end, we focused on the Trail Making Test Part A and B (TMTA; TMTB) and Object Alternation (OA). TMTA, a measure of attention and information processing speed, involves rapidly connecting consecutively numbered circles. TMTB, an executive function task, requires rapidly connecting alternating numbers and letters in sequence (16). Performance is measured in time (i.e., seconds) to completion.

OA is another executive test that relies on the ability to establish and maintain set based on visual and auditory feedback (18,28). OA in the present study was computerized and consisted of the computerized presentation of a red circle and a blue square on each trial. Participants were instructed to find the star hidden under either the red circle or the blue square with aforementioned feedback providing clues as to the object of the game – alternate between the two objects and get the star every trial. OA concluded upon the completion of 10 consecutively correct trials or maxed out at 50 trials. The dependent variables were trials to completion, number of perseverative errors relative to total trials to completion and average reaction time per trial.

Statistical Analysis

Demographic, clinical, and network variables were analyzed for between-group differences using an independent sample t-test for continuous variables and chi-squared test for categorical variables. Levene's Test for Equality of Variances were used for all t-tests (15). Bivariate correlations were used to analyze the relationship between network efficiency measures and age both regardless of age and by group. Local efficiency correlation analyses – given the number performed in comparison to the global efficiency analyses – were adjusted for multiple comparisons using the false discovery rate (4) with a significance threshold set at $q < .05$. Additionally, two-tailed partial correlations were used to examine the relationship between network efficiency and depression severity, as well as network efficiency and cognitive function (adjusting for age, sex and predicted verbal IQ) both regardless of and by group distinctions. All statistical analyses were performed in the SPSS software, version 18.0 (SPSS, Somers, NY).

Results

Between-Group Comparisons

The clinical and demographic characteristics are summarized in Table 1. There were no significant differences in age, sex distribution, or predicted verbal IQ scores. There were no significant differences between in any global or local efficiency measures. Depressed subjects performed significantly worse on the OA task with more trials to completion, longer reaction times, and more errors per trial. There were no significant differences on Trails A or B performance.

Global Network Efficiency and Age

The three global efficiency measures were significantly correlated with other (E_{native} and E_{norm} : $r = .307$, $p = .005$, $df = 81$; E_{native} and E_{int} : $r = .809$, $p < .0001$, $df = 81$; E_{norm} and E_{int} : $r = .381$, $p < .001$, $df = 81$). All measures of network efficiency were significantly associated age. E_{int} demonstrated the largest negative association ($r = -.425$, $p < .0001$, $df = 81$; Figure 1), followed by E_{native} ($r = -.410$, $p < .0001$, $df = 81$) and normalized global efficiency ($r = -.310$, $p = .003$, $df = 81$). These correlations remained significant by subject group. Thus, in healthy comparison subjects, age was associated with native and integrated global efficiency ($r = -.496$, $p = .001$; $r = -.416$, $p = .006$, $df = 41$) and not associated with normalized global efficiency ($r = -.299$, $p = .052$, $df = 41$). In MDD, all three measures were significantly correlated with age (E_{native} : $r = -.348$, $p = .028$; E_{norm} : $r = -.314$, $p = .048$, E_{int} : $r = -.423$, $p = .007$, $df = 38$).

Global Network Efficiency and Depression

Across the entire sample, there were no significant correlations between efficiency measures and depression severity. When analyzed by group, only normalized global efficiency was negatively correlated with depression severity within the depressed sample ($r = -.343$, $p = .033$, $df = 37$).

Global Network Efficiency and Cognitive Function

Integrated global efficiency was significantly associated with OA trials to completion ($r = .255$, $p = .028$, $df = 72$), reaction time ($r = .254$, $p = .029$, $df = 72$), and errors per trial ($r = .273$, $p = .018$, $df = 72$). Native global efficiency was only significantly correlated with OA errors per trial ($r = .315$, $p = .006$, $df = 72$). These overall sample correlations were driven by the depressed group as there were no significant correlations between cognitive and global efficiency measures in healthy comparison subjects. Thus, in the depressed group, both native and integrated global efficiency were significantly associated with OA trials to

completion (E_{native} : $r = .370$, $p = .024$, $df = 34$; E_{int} : $r = .427$, $p = .009$, $df = 34$) and OA errors per trial (E_{native} : $r = .483$, $p = .003$, $df = 34$; E_{int} : $r = .427$, $p = .009$, $df = 34$). There were no significant correlations with any global efficiency measures and TMTA and TMTB.

Local Network Efficiency

Across the total sample, local efficiency correlated with age in predominately temporal regions, as well as bilateral precentral cortex and the right rostral middle frontal gyrus in the dorsolateral prefrontal cortex (Figure 2a). In HC subjects, age was negatively associated with local efficiency in the left entorhinal cortex, right precentral gyrus, and bilateral fusiform gyri (Figure 2b). In MDD subjects, bilateral hippocampal local efficiencies were associated with age (Figure 2c). There were no significant correlations between E_{loc} and depression severity or cognitive measures.

Discussion

To our knowledge, this is the first study to examine differential results of specific network efficiency metrics let alone within the context of clinical/cognitive correlates in major depression. Consistent with previous studies (26), we found that global network efficiency declines with age in both healthy controls and depressed subjects. Normalized global efficiency was the only measure to exhibit declines with increasing depression severity and only in depressed subjects. This was despite no between-group differences in this metric. Results may reflect the fact that the normalization associated with this global efficiency measure adjusts for fundamental organizational network properties like randomization; an aspect of network disorganization that may be more prevalent in individuals with depression. By controlling for this randomization, results for normalized global efficiency revealed a negative relationship between depression severity and global efficiency. In contrast, this same depressed group showed a positive relationship between native as well as integrated network efficiency and poor performance on the OA task. This highlights the differential associations of the various global efficiency measures examined in the present study as they relate to clinical populations' overall behavioral presentation.

In depressed subjects, both E_{native} and E_{int} were positively associated with poor performance on the OA task with E_{int} associated with all aspects of performance and E_{native} associated with errors relative to total trials only. This provides evidence that in the context of major depression, increased network efficiency is a reflection of a more random network that could explain poor performance. Global network efficiency reflects different aspects of underlying network organization depending on clinical and cognitive context. For example, in depression, increased network efficiency may represent a tendency towards a more random organization. Optimized brain networks have a balance of integration (combining distributed functions) and segregation (separating distributed functions). If additional network connections are not organized according to function, random networks can have increased efficiency or network integration at the cost of decreased network segregation. Further suggestive of this notion is that *gamma*, a measure of network segregation (22), was negatively correlated with OA trials to completion ($r = -.372$, $p = .026$, $df = 34$) and OA errors per trial ($r = -.429$, $p = .009$, $df = 34$) in depressed subjects.

Focusing on local efficiency, our primary findings demonstrated significant correlations with age – predominately within temporal lobe regions for the entire group. It should be noted, however, that the breakdown of affiliated regions differed based on the presence or absence of a clinically diagnosed depression. For example, local efficiency declined with age in bilateral hippocampal regions in major depression while more subtle alterations in the entorhinal cortex were seen in healthy controls. Previous studies in aging populations would suggest that hippocampal complex findings – particularly as they relate to behavioral

manifestations of learning and memory deficits – are only seen in the presence of pathological entities such as dementia and/or depression (13). Our work with network efficiency metrics would suggest that local efficiency measures derived from graph theory may be more sensitive to alterations in hippocampal subregions than more traditional measures of brain structure. The association to learning and memory remains to be determined but holds promise given the strong *r*-values displayed in our healthy control group. The decreased local efficiency seen in these vulnerable temporal regions can be conceptualized as a reduction in network segregation or less functional specialization. Consistent with this notion, one of the brain regions that declined with age in healthy comparison subjects, the fusiform gyrus, has been shown to exhibit less stimulus-specific activation (namely, faces) with age (19).

In conclusion, while all measures of global efficiency significantly correlated with age, not all measures of global efficiency correlated with behavior. It follows that not all global efficiency metrics derived from graph theory are equivalent. Thus, the interpretation of network-based measures across the lifespan depends on the age and the clinical characteristics of the sample under study as well as the cognitive/affective functions being measured. Furthermore, several local metrics of hippocampal efficiency may prove valuable in preclinical states of pathological aging – an area of increased study with the advent of NIH-based initiatives to understand this predominantly mid-life state (5). In sum, our study highlights the importance of acknowledging the clinical and cognitive context within which network-based metrics of neuroimaging are to be used in various aging populations.

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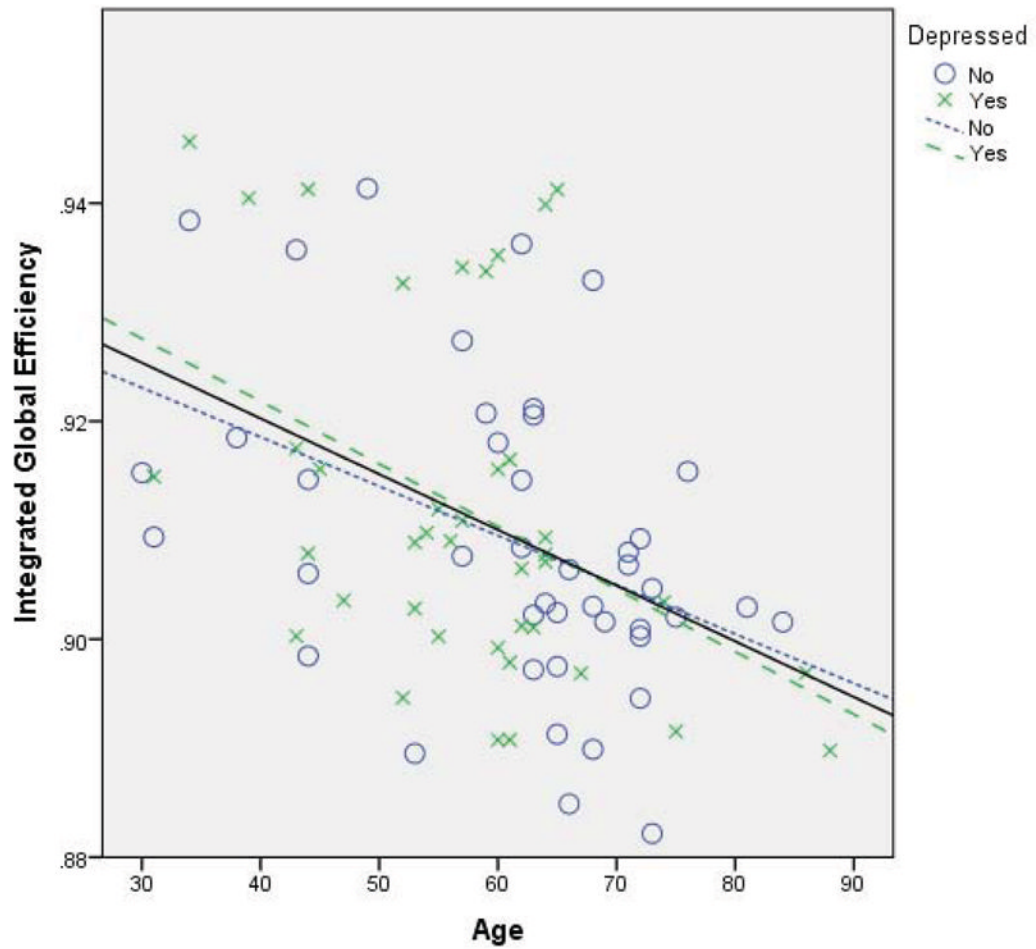


Figure 1. Integrated global efficiency correlated with age
 Correlation of age and integrated global efficiency. Age was negatively associated with integrated global efficiency in both subject groups (healthy comparison: dotted line; major depression: dashed line) and the total sample (solid line).

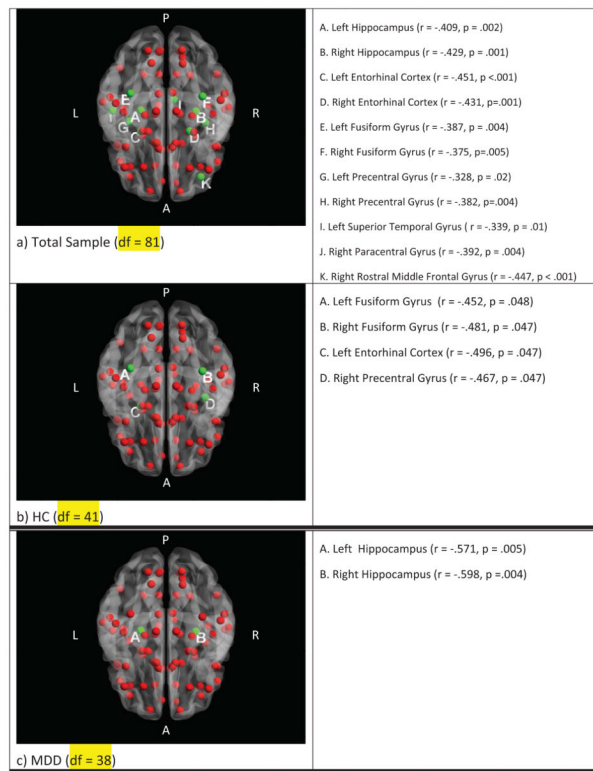


Figure 2. Local efficiency correlated with age

Correlation of age and local efficiency on an inferior view of the brain (A: Anterior, P: Posterior, L: Left, R: Right). a) Total sample, b) HC: healthy comparison group, c) MDD: major depression group. All nodes indicated in red, significantly associated nodes after false discovery rate correction are indicated in green. Each node represents a Freesurfer-defined brain region with the node placed at the coordinates of each brain region's centroid.

Table 1

Network Efficiency Measures

Global and local efficiency measures reflect network integration, while local efficiency reveals network segregation. Results for significant associations with age, depression, and object alternation (OA) performance are summarized.

Measure	Description	Interpretation	Age	Depression	OA performance
Native Global Efficiency (E_{native})	Efficiency of information transfer in the unthresholded network	Network Integration	↓	----	↓ (in MDD)
Normalized Global Efficiency (E_{norm})	Efficiency of information transfer in the unthresholded network divided by the efficiency of a random network of equal size	Network Integration	↓	↓	----
Integrated Global Efficiency (E_{int})	Efficiency of information transfer in the network as a function of network cost	Network Integration	↓	----	↓ (in MDD)
Local Efficiency (E_{loc})	Efficiency of information transfer between a node and neighboring network nodes	Network Segregation	↓ (in prefrontal, temporal cortex)	----	----

Table 2

Subject Characteristics

Subject groups did not differ on age, sex distribution, years of education, or predicted verbal IQ. As expected, depressed subjects had significantly higher depression rating scores (HAM-D: Hamilton Rating Scale for Depression; CES-D: Center for Epidemiological Studies Depression Scale). There were no differences in global efficiency measures. Cognitive measures are represented by z-scores. Depressed subjects performed significantly worse on the object alternation (OA) task.

	HC	MDD	t	df	p-value
N	40	43			
Age	61.3 (13.1)	57.4 (11.9)	1.442	81	.153
Gender (M/F)	17/26	13/27	$\chi^2 = .444$	1	.505
Education (years)	15.7 (3.11)	14.7 (2.79)	1.54	81	.128
HAMD	.88 (1.3)	19.03 (2.83)	-37.06	53.75	<.0001
CESD	4.53 (4.71)	31.15 (8.54)	-17.23	57.88	<.0001
Predicted Verbal IQ	108.68 (11.93)	105.28 (12.32)	1.27	79	.21
Native Global Efficiency	151.76 (36.67)	165.75 (58.24)	-1.3	64.88	.2
Normalized Global Efficiency	.95 (.03)	.96 (.03)	-1.26	81	.212
Integrated Global Efficiency	.91 (.01)	.91 (.02)	-.882	81	.381
Trail Making Test A	0 (1.0)	-.07 (1.2)	F = 1.06	1,72	.306
Trail Making Test B	0 (1.0)	-.11 (1.0)	F = .263	1,72	.61
OA trials to completion	0.02 (1.0)	.59 (.66)	F = 8.78	1,72	.004
OA reaction time	0 (1.0)	.51 (.75)	F = 6.44	1,72	.013
OA errors/trial	0 (.99)	.51 (.81)	F = 5.8	1,72	.019