Structural Network Alterations Induced by ART-naive and ART-treated Subjects Infected with HIV

Jiaojiao Liu

Beijing You'an Hospital, Capital Medical University

Wei Wang

Beijing You'an Hospital, Capital Medical University

Yuanyuan Wang

Beijing Second Hospital

Mingming Liu

Cangzhou Central Hospital

Dan Liu

Beijing You'an Hospital, Capital Medical University

Ruili Li

Beijing You'an Hospital, Capital Medical University

Quansheng Gao

Institute of Environment Medicine and Occupational Medicine, Academy of Military Medicine

Hongjun Li (✉ lihongjun00113@126.com)

Institute of Environment Medicine and Occupational Medicine, Academy of Military Medicine

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Abstract

Background

To investigate how the structural connectivity altered in cART-treated HIV patients and cART-naïve HIV patients by conducting Network analysis of Diffusion Tensor Imaging (DTI) data.

Methods

We enrolled 22 cART-naïve, 23 cART-treated and 28 normal controls in our current study. Firstly, the DTI imaging data pre-processing was conducted and the asymmetric 90×90 matrix for each participant from their DTI data was obtained with the use of PANDA. Then, we applied a graph-theoretical network analysis toolkit, GREYNA v2.0, to calculate metrics such as small-“worldness,” characteristic path length, clustering coefficient, global efficiency, local efficiency, and nodal “betweenness”. Finally, we took comparisons among the three groups to investigate topological alterations, and we also conducted relevant analysis with current CD4 T cell counts and neuropsychological evaluation.

Results

Results (1) the regional characteristics (nodal efficiency) were altered in CART- and CART+ patients predominantly in the frontal cortical regions; (2) changes in various network properties in CART- and CART+ patients were associated with the performance of behavior functions; (3) Reduced network segregation was associated with lower current CD4 count in cART- participants, suggesting that brain network segregation may be adversely affected by a history of greater immune suppression. (4) Hubs redistributed in HIV subjects especially in cART+ patients.

Conclusion

1) The regional characteristics (nodal efficiency) were altered in cART-naïve and cART-treated patients predominantly in the frontal cortical regions; (2) changes in various network properties in cART-naïve and cART-treated patients were associated with the performance of behavior functions; (3) reduced network segregation was associated with lower current CD4 count in cART-naïve participants, suggesting that brain network segregation may have been adversely affected by a history of greater immune suppression. (4) Hubs redistributed in HIV subjects especially in cART-treated patients.

Background

The human immunodeficiency virus (HIV) invades the central nervous system(CNS) Shortly after seroconversion (~ 8 days) following significant immune suppression and notable cognitive impairment. [1] Combination antiretroviral therapy (cART) has been reported to have extensively decreased the morbidity and mortality of HIV-infected individuals and extended their life expectancy, but HIV-associated neurocognitive disorders (HAND) are still prevalent.[2–4] Currently, it is not fully understood why cognitive impairment persists in HIV infected subjects who have been virologically suppressed for several years.[5–

8] One possible interpretation may be that irreversible CNS impairment takes place quite early after HIV infection, which causes subtle cognitive alterations measurable by comprehensive neuropsychological tests. In such case, cART would effectively prevent the progression of CNS damage but not reverse occurred injury.[9] However, there are also HIV patients with normal cognition even after long term HIV infection with cART. By studying their injury characteristic may help in our further understanding the pathomechanism of HIV infection.

Nowadays, noninvasive magnetic resonance imaging (MRI) provides idle measures to detect early alterations in HIV infected subjects. As one of them, Diffusion tensor imaging (DTI) is capable of detecting and measuring white matter integrity and fiber connectivity in vivo. Previous studies have found extensive white matter impairments (including corticospinal tracts, the cerebral peduncle, the cerebellar peduncles, the internal capsule, the uncinated fasciculus, the corona radiata and the corpus callosum (CC) etc).[10–15] The combination of graph theory and DTI analysis, has provided interesting insights into the organization of the complex and comprehensive brain network. Network analysis based on the white matter network has shown that HIV-positive participants presented with disrupted global and nodal connectivity in structural connectome,[16, 17] preferential alterations in clustering coefficient, path length, and local efficiency, indicative of structural segregation and structural integration. However, little is known about how network metrics change in HIV-positive individuals with normal cognition after regular cART, and what the differences are between the so-called “cognition-negative” and the healthy controls.

In our study, we initially combined DTI-based tractography and graph theoretic methods to explore global and nodal alterations among three groups: HIV-positive subjects with regular cART treatment. HIV-positive naive to treatment, and HIV-negative controls, aimed at investigating differences of topological organization among three groups. By doing so, we not only discovered effective biomarkers for earlier diagnosis, we also could monitor the effect of cART on HIV-positive individuals. We then examined the associations between network metrics and cognitive performance. We hypothesized that except for the path length, topological metrics would show positive correlations with the cognition. Moreover, the cART group may not have displayed a better result due to the existing brain damage.

Methods

Subjects and data acquisition

From March 2016 to November 2016, a total of 73 subjects: 22 cART-naïve, 23 cART-treated, 28 normal controls, were recruited at Capital Medical University Beijing You An Hospital in China. This study was approved by the Ethics Committee of Beijing You An Hospital. All the Participants had submitted a written, signed, and dated informed consent after acknowledging of this study. The exclusion criteria for HIV subjects included: history of alcohol or substance abuse, history of neurodegenerative disease except for HIV (including Alzheimer's disease), diagnosis of neurological comorbidities (including leukoencephalopathy or HIV encephalitis), obvious brain lesion (including tumors or trauma), The clinical markers, such as current CD4 + cell counts, CD4+/CD8 + ratios, and plasma viral loads were collected for

all patients. The duration of HIV infection was confirmed by patients' self-reports. The NC subjects were recruited from the same urban regions as the patients. The exclusion criteria for NC subjects included: obvious brain lesions (such as trauma or tumors), any history of previous neurodegenerative diseases (such as diabetes, and Alzheimer's disease), or other systemic diseases.

Neuropsychological evaluation

The Neuropsychological test conducted for each participant had been validated for HIV positive populations. The following six competency areas were evaluated with reference to the Frascati guidelines: (1) speed of information processing using the tracking test part A; (2) use of the same pair of continuous performance tests (CPT-IP), Wechsler memory Table III (WMS-III), pacing auditory serial addition (PASAT) for attention/working memory; (3) motor function using grooved nail plate test; (4) using Wisconsin Card Sorting Test-64 (WCST-64 Abstract/execution function; (5) learning and recall using the revised Hopkins Language Learning Test (HVLTR); short visual space memory test revision (BVMTR); (6) using category Fluency and language/language for animal naming tests. To further assess cognitive functions, composite cognitive scores were created to evaluate the six domains tested. The raw scores for each test were normalized to T scores and adjusted for age, gender, and education. The T scores of each cognitive domain in one or more tests are averaged over the domain to calculate a T score for a particular domain and then further applied to the correlation analysis. Additionally, cognitive impairment is diagnosed as ANI in patients with at least two cognitive domains that exhibit at least 1 SD below the mean of neuropsychological testing.

Image acquisition

For each participant, both T1-weighted MRI and DTI were obtained on a 3.0T Siemens scanner (Allegra, Siemens Medical System, Erlangen, Germany) using a 32-channel phased array coil. A standard birdcage head coil and restraining foam pads were used to minimize head motion. A Structural T1-weighted MRI was acquired with a spoiled gradient recall sequence with the following parameters: Slices = 176, TR = 1900 ms, TE = 2.2 ms, inversion time (TI) = 900 ms, FA = 9°, field of view (FOV) = 256 × 256 mm, acquisition matrix = 256 × 256, and thickness = 1 mm. For DTI, we used single shot echo planar imaging (EPI) sequences in contiguous axial planes covering the whole brain with the following parameters: in 32 independent, non-collinear directions of a b-value = 1000s/mm² and one additional image with no diffusion weighting (b = 0), slices = 60, TR = 11000 ms, TE = 98 ms, FA = 90°, FOV = 256 mm × 256 mm, acquisition matrix = 128 × 128, and thickness = 2 mm.

Image processing

Imaging processing and network construction was performed on PAND, procedures include: Data converts from DICOM to NIfTI; the correction of Eddy current and head motion of FDT diffusion imaging data; the brain structure and tissue extraction; Realignment; the calculation of Fractional anisotropy; Diffusion tensor tractography. Tractography was operated to construct 3-D streamlines which was representative of fiber tract connectivity.[18]

Network metric construction

Firstly, according to the anatomical automatic labeling atlas, the white matter brain network was constructed by calculating the paired Pearson relative coefficients between 90 regions of interest[19]. Further, whole-brain and regional network topological properties (including small-worldness(σ), global efficiency (E_g), clustering coefficient (C_p), nodal betweenness (B_{nod}), characteristic path length (L_p) and local efficiency (E_{loc})) were calculated.

Statistical Analysis

We conducted statistical analysis with SPSS v20.0. All the demographic data and neuropsychological scores except for sex variables (with a Pearson chi-square test) were examined with the use of one-way ANOVA. Group effects of global and regional network metrics were performed among 3 groups using one-way ANOVA. Further, we explored the correlations between network measures and neuropsychological scores by partial correlation analysis with demographic variables, as covariates.

The nodes with significant group differences were performed in order to identify the correlation between neuropsychological test scores with specific brain regions.

Results

Global topology of the white matter connectome

All the three groups did not present significant small-world organization. ANCOVAs showed that there are no significant group effects on global efficiency($P = 0.380$), characteristic path length($P = 0.279$), and clustering coefficient($P = 0.433$).

Regional characteristics in anatomical brain networks in CART-, cART-treated and control patients

The regional alterations in cART-treated, cART-naïve and NC networks were found to have significantly altered nodal characteristics (i.e., betweenness centrality, local efficiency, path length, and clustering coefficient) in cortical regions, which were mainly located in the right hemisphere. We found that betweenness alterations predominately located in the prefrontal lobe (e.g., OLF and SFGmed) and temporal lobe (e.g., TPOsup)(Fig. 1). We also found that clustering coefficient widely described across occipital (e.g., LING), parital (e.g., POCG), subcortical (e.g., CAU) and prefrontal (e.g., SFGmed)lobes(Fig. 2). In addition, significant local efficiency differences mainly concentrate on subcortical (e.g., CAU) and prefrontal (e.g., SFGmed) lobes(Fig. 3). Finally, path length changes were all discovered in pareital lobes (e.g., POCG, PCG, SPG, IPL)(Fig. 4)

Differences in betweenness centrality, local efficiency, path length and clustering coefficient

There were no significant changes among the three groups. ANOVAs presented significant group differences in betweenness connectivity, path length, clustering coefficient, and local efficiency. We

further localized the nodes with changed betweenness centrality among the three groups. Regions with significant differences across the three groups were located in left TPOsup, right SFGmed and OLF. Post hoc tests showed an increase in SFGmed in cART-treated group and TPOsup in cART-naïve group versus the control group. In addition, a decrease in OLF in the CART- group than cART-treated (Fig. 1)

We also investigated the nodes with alternated clustering coefficient and excitedly we found significant changes in nodes located in left POCG, right LING, CAU, and SFGmed. Also, the following post hoc test indicated an increase in left POCG and right LING in cART-treated and cART-naïve than control. Increases in CAU were also found in CART-naïve than in cART-treated. On the other hand, decreases were found in SFGmed in cART-treated and CART-naïve group versus the control. (Fig. 2)

As for the local efficiency, we interestingly discovered that nodes that lied in left ACG, right CAU and SFGmed displayed significant transformation. However, the post hoc test only prompted an increase in SFGmed and CAU in control group compared with cART-treated group. Furthermore, there was a decrease in CAU in cART-treated verus in the cART-naïve. (Fig. 3)

Finally, the significant length path changes mainly concentrated on the right part of the brain, for instance, PCG, POCG, SPG and IPL. The post hoc test indicated an increase in PCG, POCG, SPG and IPL in the cART-treated group versus in the control group. Otherwise, there was a decrease in the cART-naïve group as compared with the cART-treated group. (Fig. 4)

Hub regions

In the control group, five regions including three hetero modal or unimodal association cortex regions, two subcortical cortex regions were identified as the hubs because of large values in betweenness (Table 2). In the cART-naïve group, 10 regions including five heteromodal or unimodal association cortex regions and four subcortical cortex regions and one temporal cortex were identified as the hubs (Table 3). In the cART-treated group, 15 regions including seven heteromodal or unimodal association cortex regions, four subcortical cortex regions, two paralimbic cortex regions and two primary cortex regions were identified as the hubs (Table 4)

Correlation between topological metrics and clinical markers

By examining the relationship between the significant topological metrics and the current CD4 T cell counts, we found that in the cART-naïve group, the left POCG in clustering coefficient was negatively correlated with the current CD4 T cell counts, while CAU in the clustering coefficient was positively correlated with the current CD4 T cell counts. However, in the cART-treated group, CAU in local efficiency was negatively correlated with the current CD4 T cell counts(Fig. 5)

Correlation between topological metrics and cognitive performances

We further examined the relationship between network metrics and cognitive performances, and dedicated that the cART-naïve changes of topological metrics were significantly associated with declined cognitive functions. We also found that cART-naïve subjects with decreased clustering coefficient (e.g., SFGmed.R, LING.R) in WM network had lower attention/working memory, speed of information processing and abstract/executive function, Also, cART-naïve subjects with decreased local efficiency of several cortical regions (e.g., SFGmed.R) in WM network had lower speed of information processing functions and abstract/executive function, while patients with longer shortest path length (e.g., PCG.R, POCG) had lower motor function. There was an extraordinary phenomenon discovered in which patients with lower local efficiency had higher memory (e.g., CAU.R)

For cART-treated patients, we saw quite the opposite result. The longer shortest length path was positively correlated with the increased speed of information processing, abstract/executive function, and attention/working memory. Increased local efficiency was correlated with lower abstract/executive function. Clustering coefficient was negatively correlated with memory. There was also an extraordinary phenomenon discovered in which the Clustering coefficient was positively correlated with motor function(Fig. 6)

Discussion

Our current study combined diffusion tensor Image and graph theory to demonstrate changes in the organization and segregation of structural networks in cART-naïve and cART-treated subjects. Our main findings were as follows: (1) the regional characteristics (nodal efficiency) were altered in cART-naïve and cART-treated subjects preferentially in the frontal cortical regions; (2) alterations in some topological metrics in cART-naïve and cART-treated patients correlated with cognitives performances; (3) reduced network segregation was associated with lower current CD4 T cell counts in cART-naïve patients, indicating that brain network segregation may have been adversely affected by a history of enhanced immunosuppression; (4) Hubs redistributed in HIV subjects especially in cART-treated patients. These findings suggested that WM degeneration altered the structural connectivity pattern of WM network in HIV individuals, and cART failed to reverse the existing disruption of structural topology. However, this may, just slow the progression, so early diagnosis and treatment are imperative.

In our study there were no significant small-worldness among the three groups, which is quite different from extensive studies[20, 21]. This may be due to our limited samples. Global differences in our study also failed to present results like previous studies. It is possible that the average time of infection was too short to present such outcomes.

The regional alterations in cART-treated, cART-naïve and NC networks were detected to have significantly altered nodal characteristics (i.e., betweenness centrality, local efficiency, path length and clustering coefficient) in cortical regions, which were mainly lied in the right hemisphere. We found that betweenness alterations preferentially lied in the prefrontal lobe (e.g., OLF and SFGmed) and temporal lobe (e.g., TPOsup). And previous studies have shown that these frontal regions exhibited HIV-related

abnormalities in the WM integrity [22–24] and gray matter morphology. The temporal pole, which includes linguistic integration, emotion, and semantic memory, also verified that there was atrophy and neuronal loss [25–29] in HIV patients and SIV infected rhesus monkeys. We also found that clustering coefficient widely described across occipital, parital, subcortical and prefrontal lobes. In addition, significant local efficiency differences mainly concentrated on the subcortical and prefrontal lobes. Finally, path length changes were all discovered in the parietal lobe.

According to most of the previous studies, a combination of shortest path lengths and high clustering coefficients gave rise to the most optimal network balance between segregation and integration[30]. However, HIV infection can be a disconnection element. Betweenness centrality measures the importance of nodes for information transmission[31]. Our findings of betweenness centrality alterations among cART-treated, cART-naïve and control groups indicated that cART-treated had significantly higher betweenness centrality than the cART-naïve group, which suggested that prescribed cART does improve structural connectivity to some extent, which is inconsistent with previous studies[32]. However, the right SFG and the right TPOsup showed increased betweenness centrality, which is quite opposite to previous research. We speculated that the increase of these nodes may be compensatory for the reduction of OLF centrality.

Clustering coefficient measures network segregation which reflects specialization of discrete brain regions or systems in conducting Specific psychological operations[33]. In our study, the right SFGmed implied an increase in Clustering coefficient in control group compared with cART-naïve and cART-treated group, suggesting a stronger local specialization, which has been verified in several studies[32]. On the other hand, there was an obvious decrease in the Clustering coefficient in the control group than the other two groups. This may be due to a possible compensation for the decrease in SFG.

Local efficiency in the right ICU and the right SFGmed in the control group was significantly higher than that in the cART-treated group, indicating that the efficiency of information transformation was affected by the white matter disruption, which is quite consistent with the previous studies.

Short path lengths in the brain networks ensure efficient transmission or rapid transfer of information between or among remote areas considered to be the basis of cognitive processes[34]. The increase in HIV-related pathways may therefore reflect the disruption of neuronal integration across distant regions associated with impaired cognitive function[35]. These findings indicated that CART may have differential effects on regional variability with regular treatment.

We further examined the relevance between network affairs and cognitive performances. Results suggested that the cART-naïve changes of network metrics were significantly associated with the decrease of cognitive functions, which is in accordance with the previous studies[36]. Meanwhile, for the cART-treated groups, we obtained quite the opposite results. The speculation for this phenomenon may be that the compensatory mechanism is reversed even during the ART era.

We further examined the relevance between network affairs and cognitive performances. Results suggested that the cART-naïve changes of network metrics were significantly associated with the

decrease of cognitive functions, which is in accordance with the previous studies[36]. Meanwhile, for the cART-treated groups, we obtained quite the opposite results. The speculation for this phenomenon may be that the compensatory mechanism is reversed even during the ART era.

Among cART-naïve patients, lower current CD4 T cell counts were positively correlated with decreased clustering coefficient (eg, right CAU), indicating that historical immunosuppression plays a key role in brain network segregation. However, lower current CD4 T cell counts were negatively associated with the reduced clustering coefficient (e.g., left POCG). That may be explained by the compensatory mechanism of the neighborhood nodes. While among cART-treated patients current CD4 T cell counts were negatively correlated with right CAU local efficiency, indicative of the reserved compensatory mechanism with the application of ART.

We investigate alterations of hub profile, which plays a crucial role in identifying the most relevant nodes to information traffic. To identify the hub regions, we examined nodal betweenness centrality of each cortical region across the three subject groups (see material and methods). We found that these identified hubs were preferentially located in regions of association cortex (PUT, STG, and MOG), indicating their paramount roles in the structural networks. When hubs among three groups were further analyzed, we interestingly found the phenomenon that hubs in the cART-naïve and cART-treated groups redistributed separately. According to the “hubs overload and failure” theory, brain disease can break down the optimal balance of network, diminishing the information handling of hub nodes. As a result, scenario rerouting and rewiring contributed to hubs overload followed by hub failure[37]. Furthermore, more hubs in cART-treated patients were reproduced from prefrontal to occipital, apart from the cognitive injury resulting from pathological affairs, the cART patients received may also lead to hub redistributed in drugs vulnerable regions, which was suspected of higher metabolic activity from these regions[38]

There are several limitations in our study. In the first place, we constructed the structural network with deterministic tractography which has been widely used in previous studies. While it failed in accurately mapping out such fibers as crossing fibers and long-distance fibers, the sample size was too small to draw an effective conclusion regarding our method, though we found significant regional alterations among the three groups. Moreover, The cross-sectional nature of our study made us unable to confirm progress of HIV and the effect of cART over time. Therefore, a longitudinal study would be beneficial in future studies.

Conclusion

In conclusion, we employed diffusion tensor MRI tractography to construct WM networks of cART-naïve, cART-treated patients and NCs. However, there was no significant small-world organization, and global differences among the three groups were not obvious. Our study showed that HIV individuals on stable cART had decreased betweenness centrality, local efficiency, clustering coefficient, and longer length path within certain nodes compared to cART-naïve. In one distance, the mixture of increased and decreased connectivity would result in alterations in network organization. Moreover, we found that the HIV subjects

had decreased nodal efficiency of cortical regions preferentially lied in the frontal lobe. Furthermore, we also found that the changes of HIV subjects highly correlated with cognitive functions. Finally, hub regions were redistributed in HIV subjects, especially in cART-treated patients. Our findings support the WM degeneration hypothesis of changed brain networks in HIV participants, and suggest that the changes influence the cognitive performances of patients. This HIV infected human brain WM networks, based on topology-based analysis, provides a new approach to show patterns of structural disconnectivity in neuropsychiatric diseases. This current study also helps us better understand human brain neurodegenerative connectome in diseases.

Abbreviations

WM White Matter

CNS central nervous system

cART combination Antiretroviral Therapy

HAND HIV-associated neurocognitive disorders

DTI Diffusion tensor imaging

MRI magnetic resonance imaging

CC corpus callosum

CPT-IP Performance Test Identical Pairs

WMS-III The Wechsler Memory Scale-III

PASAT Paced Auditory Serial Addition Test

WCST-64 Wisconsin Card Sorting Test-64

HVLT-R Hopkins Verbal Learning Test–Revised

BVMT-R Brief Visuospatial Memory Test–Revised

ANI Asymptomatic neurocognitive impairment

FN fiber number

FA fractional anisotropy

Lp path length

Cp clustering coefficient

Eg global efficiency

Eloc local efficiency

Bnod nodal betweenness

LING Lingual gyrus

POCG Postcentral gyrus

CAU Caudate nucleus

SFGmed Superial frontal gyrus

SPG Superior parital gyrus

OLF Olfactory cortex

SFG Superior parital gyrus

TPOsup Temporal pole

Declarations

Ethics approval and consent to participate

This research was reviewed and approved by the Ethics Committee (seal) of Beijing You'an Hospital, Capital Medical University.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Jiaojiao Liu and Hongjun Li designed the paper, Jiaojiao Liu Wrote the paper, Weiwang, Yuanyuan Wang, Mingming Liu, Ruili Li collect the data, Dan Liu participated in the data analysis, Hongjun Li and Quansheng Gao reviewed the paper.

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Tables

Table 1 Demographic and neuropsychological evaluation of CART-, CART+ patients and normal controls

Items	CART+ patients	CART- patients	NC subjects	P value
N	23	22	28	NA
Age (year)	30.27 ± 7.48	31.96 ± 7.00	32.04 ± 4.51	0.566
Gender (Female/Male)	22/1	1.00 ± 0.21	1.07 ± 0.26	0.46
current CD4 T cell counts (cell/μL)	548.14 ± 136.33	536.28 ± 228.74	NA	0.715
CD4/CD8 ratios	0.74 ± 0.58	0.65 ± 0.3	NA	0.74
Verbal and language score	51.14 ± 5.78	40.35 ± 6.48	NA	0
[Attention/working memory score]	45.14 ± 5.53	41.40 ± 11.73	NA	0.187
[Abstract/executive]score	61.20 ± 7.66	54.12 ± 10.56	NA	0.15
Memory (learn and recognition)score	45.83 ± 5.80	39.38 ± 7.68	NA	0.004
Speed of information processing score	48.64 ± 8.20	43.15 ± 9.94	NA	0.057
Motor score	49.16 ± 8.50	45.65 ± 10.23	NA	0.232

Table 2 Regions showing high betweenness in cortical networks of normal subjects

Regions	Class	betweenness
Left Precuneus	Parital	442.58
Right Precuneus	Parital	290.30
Left Putamen	Subcortical	339.32
Left Thalamus	Subcortical	266.60
Right Superior temporal gyrus	Temporal	222.53

Table 3 Regions showing high betweenness in cortical networks of CART- subjects

Regions	Class	betweenness
Left cuneus	Occipital	237.42
Right Superior occipital gyrus	Occipital	274.90
Left Middle occipital gyrus	Occipital	231.16
Left Precuneus	Parital	466.01
Right Precuneus	Parital	377.92
Right Caudate nucleus	Subcortical	227.52
Left Putamen	Subcortical	346.68
Right Putamen	Subcortical	459.87
Left Thalamus	Subcortical	289.33
Right Superior temporal gyrus	Temporal	250.48

Table 4 Regions showing high betweenness in cortical networks of CART+ subjects

Regions	Class	betweenness
Right Precentral gyrus	Frontal	252.46
Right Supreior frontal(dorsolateral)	Prefrontal	230.69
Right Supreior frontal gyrus(orbital part)	Prefrontal	259.38
Right Supplementary motor area	Frontal	264.91
Light Supreior frontal gyrus(middle orbital)	Prefrontal	322.54
Left Calcarine fissure and surrounding cortex	Occipital	230.20
Left Middle occipital gyrus	Occipital	396.98
Left Precuneus	Parital	327.69
Right Precuneus	Parital	386.22
Left Paracentral lobule	Parital	252.64
Left Putamen	Subcorticle	489.17
Right Putamen	Subcorticle	431.40
Left Thalamus	Subcorticle	217.11
Right Thalamus	Subcorticle	364.56
Right Supreior temporal gyrus	Temporal	236.58

Figures

Figure 1

regions with significant differences in betweenness centrality among the three groups. The nodes marked in the map represents the significant differences among the three groups. For each node, the bar and error bar indicate the mean value and standard error, respectively. Post hoc tests showed increase in SFGmed in CART+ group and TPOsup in CART- group than control group. In addition, decrease in OLF in CART- group than CART+. *P<0.05. **P<0.01.

Figure 2

regions with significant differences in clustering coefficient among the three groups. The nodes marked in the map represents the significant differences among the three groups. For each node, the bar and error bar indicate the mean value and standard error, respectively. Post hoc tests showed increase in left POCG and right LING in CART+ and CART- than control. Increase in CAU in CART- were also found in CART- than in CART+. On the other hand, decrease in SFGmed in CART+ and CART- group than control. *P<0.05. **P<0.01.

Figure 3

regions with significant differences in local efficiency among the three groups. The nodes marked in the map represents the significant differences among the three groups. For each node, the bar and error bar indicate the mean value and standard error, respectively. Post hoc tests showed increase in SFGmed and CAU in control group compared with CART+ group. Besides, decrease in CAU in CART+ than in CART-. *P<0.05. **P<0.01.

Figure 4

regions with significant differences in path length among the three groups. The nodes marked in the map represents the significant differences among the three groups. For each node, the bar and error bar indicate the mean value and standard error, respectively. Post hoc tests showed increase in PCG, POCG, SPG and IPL in CART+ group than in control group. Otherwise, decrease in CART- group compared with CART+ group. *P<0.05. **P<0.01.

Figure 5

The relationship between topological metrics and clinical markers

Figure 6

The relationship between network properties and the cognitive and memory performances in cART-naive group

Figure 7

The relationship between network properties and the cognitive and memory performances in cART-treated group