White matter network abnormalities are associated with cognitive decline in chronic epilepsy

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Introduction

Patients with chronic epilepsy frequently develop co-morbid cognitive problems, ranging from memory deficits and mental slowing, to global cognitive deterioration [1]. There is a recent consensus that cognition results from the interaction between brain areas in large-scale networks [2, 3], and does not originate from a single, narrowly circumscribed brain region. Indeed, there is evidence from MRI studies on both structural [4] and function networks [5], that network efficiency plays an important role in intelligence. Epilepsy patients might have widespread network abnormalities outside of the epileptic zone [6], which might affect a variety of cognitive functions and global intelligence. The relation between deviant white matter connectivity and global intelligence (and intellectual decline) was investigated in a group of patients with chronic epilepsy with varying degrees of cognitive impairment. We used graph theoretical analysis [7] and fiber tractography to study tract volume weighted networks. We hypothesized that, 1) patients show abnormal white matter volume network properties compared to controls, 2) white matter volume network properties are related to cognitive performance in patients with chronic epilepsy.

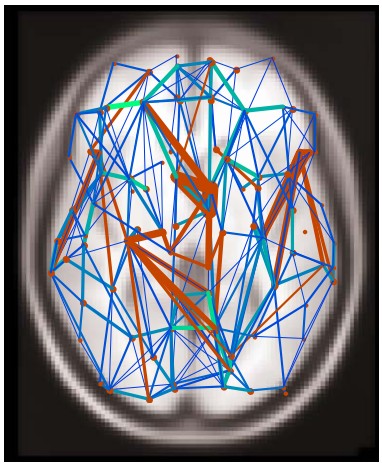

Fig. 1: *Population average volume weighted structural network. Edge thickness and color relate to volume of the tract (green is larger). Red edges have smaller volumes in the patient group (p<0.05). Dots denote location of brain regions.*

Methods

Subjects: 39 patients (19 men, 20 woman, age 40±12y, IQ 95±15) with non-symptomatic localization-related epilepsy and 23 age-matched healthy controls (9 men, 14 women, age 40±13y, IQ 113±15) were included. All subjects had a neuropsychological assessment, including assessment of IQ. The patient were classified into a cognitively non-impaired (n=32) and an impaired (n=7) group based on an estimation of their pre-morbid IQ and IQ discrepancy. **MRI:** Diffusion tensor imaging (DTI) data was acquired on a 3T MRI system (voxel size=2×2×2 mm, TE=62 ms, TR=6600 ms, SENSE=2, 15 directions at b=800 s/mm2, one b=0 s/mm2). For anatomic reference a 3D T1 scan was made (TR=9.91ms, TE=4.6ms, TI=3s, FA=8°, voxel size 1x1x1 mm). Volumes of a large number of fiber tracts were calculated from tractography through a number of processing steps (i) fitting of a tensor model incorporating uncertainty in fiber orientation [9], (ii) probabilistic tractography of a large number of fiber tracts, (iii) registration of n=90 cortical and sub-cortical regions (AAL atlas) to the individual brain, (iv) network construction by calculating the volume of each tract connecting any two regions. Last, only fiber tracts that could be reconstructed in all subjects were analyzed (k=1224). **Structural connectivity:** From the tract volume weighted networks the (weighted) cluster coefficient (C) and (weighted) path length (L) were calculated. C and L were compared between the control, non-impaired and impaired patients (Student's t-test) and partial correlation analysis (corrected for age and gender) between C and L and IQ were performed.

Results

C was significantly lower for the impaired patient group compared to the control group ($p<0.035$) and the non-impaired group ($p<0.023$). The impaired patient group had significantly higher L compared to the control group ($p<0.056$) and the non-impaired group ($p<0.04$). C was significantly and positively associated with FSIQ when corrected for age and gender ($r=0.582$, $p<0.001$), L was significantly and negatively associated with FSIQ when corrected for age and gender ($r=-0.567$, $p<0.001$). An estimate of pre-morbid IQ was also found to be significantly and positively correlated with C ($r=0.371$, $p<0.028$) and negatively correlated with L ($r=-0.312$, $p<0.068$), while controlling for age and gender. However, as hypothesized, the group differences and associations with IQ could not be localized to specific regions: no connections showed significant differences or correlations when Bonferonni corrected for multiple comparisons (Fig. 1). We found no significant relation between whole brain white matter volume and IQ in our population.

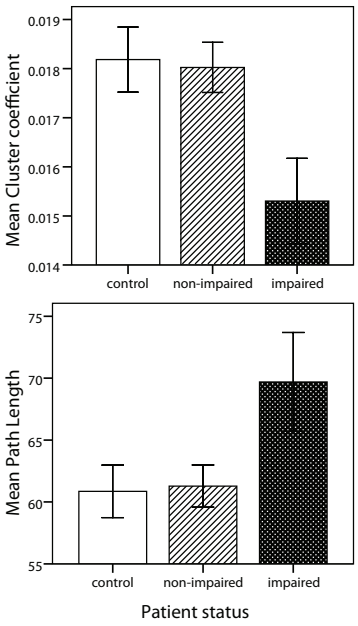

Fig. 2: *Graphs showing mean L and C for the different groups, error bars are ±1 SE.*

Discussion & Conclusion

This study reveals neurobiological evidence for impaired white matter connectivity which is related to cognitive co-morbidity in patients with chronic epilepsy. Clustering and path lengths appeared abnormal in epilepsy patients with cognitive impairment and were strongly correlated with IQ and IQ discrepancy scores. Additionally, whole brain white matter in itself was not correlated with IQ. Critically, it is not the total volume of the white matter that is deviant in epilepsy patients or associated with FSIQ, but it is the network topology, in terms of volume contribution of different white matter fiber bundles, that is abnormal in epilepsy patients and is associated with FSIQ and IQ discrepancy. Here, we demonstrate that graph theoretical analysis of whole brain networks allows us to detect subtle abnormalities in network topology, which are otherwise undetectable due to the heterogeneity of the study population and the multivariate nature of the connectivity data. Our results imply that in-vivo measurements of brain network efficiency are sensitive markers for cognitive decline in chronic epilepsy.

Partial correlation table, controlled for age & gender

		FS-IQ	Pre-morbid IQ	IQ discrepancy
Cluster Coefficient	r	0.582	0.519	0.371
	p-value	*0.000*	*0.001*	*0.028*
Path Length	r	-0.567	-0.534	-0.312
	p-value	*0.000*	*0.001*	0.068

Table 1: *Partial correlation table showing correlation values between C and L and FS-IQ, Pre-morbid IQ and IQ discrepancy, controlled for age and gender*

References

[1] Oyegbyle, Epilepsia, 2006; [2] Bressler & Menon, TICS, 2010. [3] Deary, NatRevNeuro, 2009; [4] Li, PLoSCB, 2009; [5] van den Heuvel, JNeuroscience, 2009; [6] Meador & Hermann, Neurology, 2010; [7] Bullmore & Sprons, NatRevNeuro, 2009