Article

The Role of Obesity in Cognitive Dysfunction in People with Epilepsy

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Summary

Objective:
In the general population, obesity is associated with accelerated age-related cognitive decline. The impact of obesity in neurological populations who already have a heightened risk of cognitive decline is unknown. This study explored the relationship between obesity and cognitive underfunction in people with medically intractable epilepsy.

Methods:
Eighty one consecutive admissions for inpatient evaluation for medically intractable epilepsy (36 Females, 45 Males) underwent tests of memory and intellectual function. Optimal level of function was assessed using the National Adult Reading Test – Revised. Measures of underfunction were calculated by subtracting current measures of intellectual ability from the NART IQ. Body Mass Index (BMI) was used as an index of obesity.

Results:
Twenty nine people had a BMI in the healthy range (36%), 31 were overweight (38%) and 21 were obese (26%). The heathy/overweight/obese groups did not differ in age at the time of assessment, age at seizure onset or optimal level of function (NART IQ). The obese group had a greater degree of suboptimal processing speed and demonstrated a greater degree of underfunction on the Full Scale IQ (FSIQ) measure compared to the healthy weight group. BMI accounted for 14% of the variance in underfunction in processing speed and 10% of the underfunction in FSIQ. Controlling for the effects of age, all measures of memory function were significantly correlated with BMI, with poorer scores associated with higher BMIs.

Significance:
A small, but significant proportion of the variance in memory function and intellectual underfunction in people with epilepsy is explained by BMI. Further work is needed to establish whether a reduction in BMI to within healthy limits is associated with improvements in cognitive function in this group.

Key words : Cognitive function, IQ, Memory, Body Mass Index,

Introduction

In the general population, obesity is associated with accelerated age-related cognitive decline from middle age onwards[1] . Non dementing adults who are obese perform more poorly on standardised memory tests compared to individuals who are a healthy weight.[2, 3] They also have smaller hippocampi [4], particularly those with central obesity[5]. Central obesity in middle age is also associated with an increased risk of developing dementia in old age [5]. The mechanisms underlying this relationship are complex and multifactorial. Obesity is a biomarker for the cardiovascular risk factors and diseases that have a direct impact on cognitive function, including diabetes and insulin resistance, elevated triglyceride levels, white matter disease, hypertension and hypercholesterolemia.[6]

The impact of obesity on cognitive function in younger neurological populations who have pre-existing, heightened risks of cognitive dysfunction is unknown. The mechanisms of cognitive dysfunction in epilepsy are complex. The underlying pathology, antiepileptic medications and psychological factors all interact with the functional reserve of an individual to shape their cognitive profile. Cognitive functions change over time, with progressive deterioration associated with frequent generalised seizures and stepwise deteriorations following episodes of status epilepticus or seizure related injuries. [7, 8]

A recent review found that the rates of obesity in people with epilepsy are similar to those found in the general population [9]. Whilst there are no associations between obesity and epilepsy type, duration, or aetiology, obesity rates are higher in patients with refractory than nonrefractory epilepsy (36.9% vs. 24.6%). Obesity is also more common in patients treated with polytherapy than those treated with monotherapy (37.7% vs. 25%). Some antiepileptic medications, particularly sodium valproate and pregabalin, have weight gain as a significant side effect [10].

This study explored the relationship between obesity and cognitive function and measures of decline on standardised indices of intellectual and memory function in people with medically intractable epilepsy. The prevalence of memory deficits in this population is already high[6], due to a combination of the underlying pathology, treatment effects and psychiatric morbidities[7] associated with the condition. We hypothesised that effects of obesity on cognitive function seen in the general population would be evident in this neurological population. This study was designed to examine the variance in measures of intellectual decline and memory function that is explained by BMI in people with intractable epilepsy.

Methods

Design:
This was a cohort study of 81 consecutive adult patients who were referred for a neuropsychological assessment at our specialist epilepsy assessment service in 2013-2014.

Participants:
All participants had a clinical diagnosis of epilepsy and were taking at least one antiepileptic medication at the time of assessment. At the time of the assessment, all participants were medically intractable i.e. they continued to experience seizures despite taking antiepileptic medications. All the participants in this study spoke English as a first language. Patients who had a diagnosis of Non Epileptic Attack Disorder (NEAD), or who were unable to complete the neuropsychological assessment due to sensory deficits or psychiatric disturbance were excluded from the study. The majority of the participants had focal epilepsy (n=77); 36 had a temporal lobe focus; 41 had an extra temporal focus or difficult to localise epilepsy; four had generalised epilepsy. All participants underwent a 3T structural MRI scan. See Table 1.

The clinical and demographic characteristics of the sample are presented in Table 2. All participants underwent a medical interview at the time of their admission to the ward which documented their medical history and all previous diagnoses. None of the participants had been given a diagnosis of sleep apnoea at the time of their assessment, but sleep studies were not conducted during their admission to investigate this possibility. One participant had a diagnosis of type 1 diabetes; none had developed type 2 diabetes. 16 participants had evidence of white matter disease on MRI. In 5 of the 16, the white matter lesions were the only abnormalities evident on MRI.

<<Table 2 about here>>

Neuropsychological Tests:
The IQs derived from the National Adult Reading Test – Revised[11] were used to provide a measure of each participants' optimal level of intellectual function. (5.8 points were subtracted to allow for the re-standardisation of the Wechsler Adult Intelligence Scale –IV - WAIS-IV).

All participants completed WAIS-IV UK Edition [12]. The Verbal Comprehension, Perceptual Reasoning, Working Memory and Processing Speed indices were used as measures of intellectual function. The list learning and list retention score from the BIRT Memory and Information Processing Battery (BMIPB)[13] were used as measures of verbal learning and recall respectively. In the list learning task the patient is aurally presented with a list of 15 words to learn over trials and is then required to recall them following exposure to a distractor list. The design learning and design recall measures from the BMIPB were used as measures of visual learning and recall respectively. In the design learning task the patient is exposed for 10 seconds to a design that has nine features and is required to reproduce it over five trials. Recall is tested following exposure to a distractor design. These tests have been described previously and have been shown to be sensitive to hippocampal pathology.[14, 15].

A measure of cognitive underfunction was calculated for each index of intellectual function by subtracting the index score from the NART IQ. In the general population BMI is negatively correlated with measures of intellectual function [16]; those with lower IQs are more likely to become obese than more able individuals [17]. In addition to underlying genetic factors, people with lower intellectual reserves, in particular deficits in executive functions, may make poorer diet choices than those

with stronger intellectual abilities [17-19]. We controlled for this pattern in our study by creating individual measures of cognitive underfunction for each participant. By subtracting each patient's current level of function from reliable measures of their optimal level of ability we ensured that the measures of intellectual underfunction we used in the analyses were relative to each patient's optimal level of function rather than the norms in the general population.

Reliable estimates of an individual's optimal memory function are not available. Measures of underfunction can only be inferred using standardised neuropsychological tests. The memory scores were converted to z scores using the means and standard deviations from published age referenced norms for each test, to allow statistical comparisons [12,13].

76 of the participants completed the Hospital Anxiety and Depression Scale yielding scores for anxiety and depression.

Body Mass Index:
All patients undergo a general health screen when they are admitted to the hospital and their weight and height is recorded. Body mass index was calculated using the following formula BMI = mass (kg)/(height (m))^2. Participants with a BMI less than or equal to 18.4 were classified as underweight. Participants with a BMI between 18.5–24.9 were classified as healthy weight. Participants with a BMI between 25 and 29.9 were classified as overweight. Participants with a BMI of 30 or over were classified as obese.

Statistical Methods:
Partial correlations, controlling for age at time of assessment, were used to examine the relationship between BMI and neuropsychological test scores. ANOVAs were used to examine the differences between the healthy, overweight and obese groups on the neuropsychological measures.

Regression analyses were used to examine the contribution of BMI to the variance in neuropsychological scores. The correlation coefficient squared (adjusted R^2) was used as a measure of the amount of variability in each memory score that was explained by the model.

Results

Body Mass Index
None of the participants were underweight; 29 had a BMI in the healthy range (36%), 31 were overweight (38%) and 21 were obese (26%). There was no difference between the three groups (Healthy vs Overweight vs Obese) in their age at the time of assessment ($F=1.3$, $df=2$, $p>0.05$), age at seizure onset ($f=0.3$, $df=2$, $p>0.05$) or optimal level of function NART IQ – ($f=0.11$, $df=2$, $p>0.05$). Similarly the three groups did not differ in their anxiety or depression scores on the HADS (Anxiety $f=0.20$, $df=2$, $p>0.05$; Depression $f=0.44$, $df=2$, $p>0.05$).
The participants with white matter lesions did not significantly differ from those without, in their BMI ($t=-1.7$, $df=79$, $p>.05$).

Epilepsy Type and Antiepileptic Medications

Epilepsy type was not associated with weight classification in this sample (Chi square = 5.6, df=5, p>0.05). See Table 1. Similarly, the number of antiepileptic medications taken was not related to the weight classifications (Chi square = 5.2, df=5, p>0.05). See Table 1. Seventeen participants were taking sodium valproate, an antiepileptic medication that has weight gain as recognised side effect. However in our sample the participants taking sodium valproate did not have a higher BMI than those who were not taking the drug (t=-0.63, df = 79, p>0.05).

Intellectual Function

The obese group demonstrated greater suboptimal function on the Processing Speed Index (f=5.8, df=2, p<0.01) and on the Full Scale IQ (f=3.6, df=2, p<0.05) compared to the healthy weight group.

Unsurprisingly, BMI was significantly correlated with age, with higher BMIs seen in the older participants (Pearson corr =0.2, p<0.05). The relationship between the measures of suboptimal function (Current level – optimal level) and BMI were therefore explored using partial correlations to control for the effects of age on BMI. BMI was significantly correlated with the degree of underfunction in processing speed (corr = -.35, p<0.01), and Full Scale IQ (-.29, p<0.01). See Table 3. BMI accounted for 14% of the variance in decline in processing speed and 10% of the variance in decline in FSIQ in this sample.

<<Tables 2 & 3 about here>>

Memory Function

All of the measures of memory function were significantly correlated with BMI. (Verbal Learning corr = -.32, p<0.01; Verbal Recall corr = -.27, p<0,01; Visual Learning corr =-.31, p<0.01; Visual Recall corr= -.19, p<0.05).

Linear regression analyses were used to determine the contribution of BMI and the measures of anxiety and depression from the HADS to the variance in the memory scores. BMI was a significant predictor in the models generated for all four memory measures. The anxiety and depression scores were not significant variables. The adjusted R^2 values were 0.13 for verbal learning, 0.09 for verbal recall, 0.08 for verbal recall, 0.09 for visual recall. See Table 4.

Discussion

BMI is correlated with the extent of underfunction on a global measure of IQ and slowed processing speed in people with medically intractable epilepsy. The more overweight the patient, the higher the discrepancy between measures of their optimal level of function and their current level of function. BMI accounts for up to 14% of the variance in slowed processing speed. Approximately ten percent of the variance in memory scores on standardised tests of verbal and visual learning can be also be explained by BMI. Our regression analyses suggest that BMI is a more powerful predictor of memory impairment than measures of anxiety and depression. Although the participants in this study all had medically intractable epilepsy, they were a heterogeneous sample in terms of their underlying pathology, type of epilepsy and anti epileptic medication regimes. Nevertheless a high BMI emerged as a significant predictor of cognitive underfunction.

With an average age in their mid-thirties, the participants in this study are significantly younger than those who are typically reported in the obesity/cognitive decline literature. This explains in part, the absence of obesity related health problems such as diabetes and sleep apnoea in this sample. However, it is noteworthy that the presence of white matter lesions was not related to BMI at this stage in the participant's life. The mechanisms driving the relationship between obesity and cognitive function in this sample are unknown and deserve further study.

Limitations:
Our measure of intellectual underfunction was based on the NART which has a restricted range in its estimates of premorbid IQ [20]. We did not have data on the educational or socioeconomic status of the participants, although these measures can also be of limited value in people whose education and employment opportunities have been limited by their condition. This was a brief pilot study, based on an audit of clinical data, designed to explore the value of this avenue of research in this patient group. Ideally cognitive decline should be measured in a longitudinal study design.

BMI is a relatively crude measure of health and does not take into account muscle mass, fat distribution or other measures of cardiovascular health and fitness. The presence of central obesity may be a particular risk factor for memory decline and accelerated hippocampal volume loss in the general population [5]. Further work is underway to examine the relationship between measures of cognitive decline in this population and more detailed measures of cardio vascular fitness including hip/waist ratio, blood pressure, eGFR and ECG data.

We did not examine dosage of individual medications as this is difficult to compare across different medications. However the prescription patterns and dosages for the majority of antiepileptic medications are not routinely adjusted for the weight of the patient and this is unlikely to account for our findings.

Interpretation:
Whilst correlation does not equate to causation, these findings suggest the possibility of cognitive improvement following a reduction in BMI in this group. In the healthy population improvements on tests of memory and executive function have been recorded following weight loss in obese individuals [4, 21, 22]. Although further work is necessary to see whether this pattern holds true in this population, this raises the possibility that lifestyle counselling could form an integral part of neuropsychological rehabilitation packages for cognitive complaints in this group.

Table 1. MRI Pathology

	Frequency	Percent
Normal: No abnormality detected	35	43.2
Hippocampal Sclerosis	12	14.8
Cortical Dysplasia	11	13.6
Dysembryoplastic Neuroepithelial Tumour	2	2.5
Structural Lesion	8	9.9
Hyper intense lesion	2	2.5
White Matter Disease	5	6.2
Surgery	2	2.5
Infarct	4	4.9
Total	81	100.0

Table 2: Clinical & Demographic Characteristics of the Participants

	Normal Weight N=29	Overweight N=31	Obese N=21
Epilepsy Type	Focal n=28 (n= 17 temporal) Generalised n=1	Focal n=30 (n= 6 temporal) Generalised n=1	Focal n=19 (n= 5 temporal) Generalised n=2
No. of AEDs	1 - n=7 2 - n=13 >2 - n=9	1 - n=3 2 - n=12 >2 - n=16	1 - n=2 2 - n=7 >2 - n=12
Age at Assessment	32.0 (10.5)	35.6 (11.0)	36.5 (10.0)
Age at epilepsy onset	18.2 (6.9)	18.2 (12.5)	15.8 (12.3)

Table 3: Relationship between BMI and Measures of Intellectual Function

	Partial Correlation with BMI (controlling for age)	R^2	% of variance explained by BMI
Verbal Comprehension Underfunction Index	Corr = -.11 n.s	0.01	1%
Perceptual Reasoning Underfunction Index	Corr = -.10 n.s	0.01	1%
Working Memory Underfunction Index	Corr =-.17 n.s	0.02	2%
Processing Speed Underfunction Index	Corr =-.36 ($p<0.001$)	0.14	14%
Full Scale IQ Underfunction Index	Corr = -.31 ($p<0.01$)	0.09	10%

n.s. not significant $p>0.05$

Table 4. Linear Regression Analyses: Memory scores as independent variables & BMI, anxiety & depression as predictor variables.

Verbal Learning Model	B	Std. Error	t	Sig.
(Constant)	67.476	6.273	10.757	.000
BMI	-.657	.216	-3.037	.003
HADS Anxiety	-.139	.355	-.392	.696
HADS Depression	-.413	.367	-1.124	.265
Visual Learning Model				
(Constant)	50.230	4.473	11.229	.000
BMI	-.500	.154	-3.241	.002
HADS Anxiety	-.356	.253	-1.408	.164
HADS Depression	.182	.261	.697	.488
Verbal Recall Model				
(Constant)	15.258	1.975	7.724	.000
BMI	-.165	.068	-2.420	.018
HADSanx	-.075	.112	-.666	.508
HADSdep	-.106	.116	-.921	.360
Visual Recall Model				
(Constant)	10.773	1.211	8.893	.000
BMI	-.100	.042	-2.391	.019
HADS Anxiety	-.086	.068	-1.249	.216
HADS Depression	-.027	.071	-.376	.708

Authors Statements

We confirm that we have read the Journals position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. The work described above conforms to the Journal's guidelines for ethical publication.

None of the authors has any conflict of interest to disclose.

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