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Type 2 diabetes and memory: Using neuroimaging to understand the mechanisms

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Abstract

The most robust and frequently reported cognitive deficits in type 2 diabetes (DM2) are those that relate to memory. Behavioural research has identified a number of potential contributory physiological factors, including abnormalities in glucose metabolism, such as hyperglycaemia and hypoglycaemia. The impact of these mechanisms on memory has been further investigated through the use of both structural and functional neuroimaging. Structural brain imaging has indicated that memory impairments in DM2 are associated with global atrophy of the brain. Further data suggest that localised atrophy in the hippocampal area, a brain region critical to memory formation and consolidation, may be primarily responsible for the memory deficits seen in this population. Functional imaging data has corroborates these findings, with functional magnetic resonance imaging (fMRI) suggesting reduced connectivity between the hippocampus and surrounding brain regions, particularly the frontal and temporal gyri. Despite this, little functional neuroimaging research has directly investigated differences in regional brain activity between healthy and DM2 participants whilst memory tasks are being performed. By using neuroimaging techniques to their full potential, we can acquire a fuller, more comprehensive picture of the impact that DM2 has on memory.

Type 2 diabetes (DM2) in older adults is associated with cognitive impairment, reflecting accelerated cognitive decline relative to that expected in normal ageing [1-3]. The most frequently reported and most robust deficits are seen in verbal episodic memory [4], although other domains of memory such as face recognition and working memory may also be affected [5, 6]. However, it is still unclear whether these deficits reflect impairments in their encoding or retrieval. These memory impairments have been attributed to varied physiological mechanisms, including abnormalities in glucose metabolism, insulin resistance, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and vascular complications [7, 8]. The role of these physiological mechanisms in neurocognitive functioning in individuals with DM2 has been investigated using a variety of neuroimaging techniques. Methods such as magnetic resonance imaging (MRI) and electroencephalography (EEG), have allowed researchers to examine both the structural and functional impact of DM2 on the brain. This review will consider these neuroimaging studies and speculate on how these innovative techniques could be informative in identifying underlying mechanisms of memory deficits in DM2.

DM2 and cognitive impairment: The mechanisms

Disturbances in glucose metabolism, including hyperglycaemia and hypoglycaemia, have been associated with cognitive dysfunction [7, 9]. Sommerfield, Deary and Frier [7] observed that induced acute hyperglycaemia in adults with DM2 impaired cognitive performance, most notably in the working memory domain. Relatively few studies have investigated the effects of chronic hyperglycaemia on memory. High glycated haemoglobin (HbA1c) levels have been associated with general cognitive and memory deficits in DM2 [10, 11], but findings are mixed. The recent ACCORD-MIND study failed to observe any benefits to working or verbal episodic memory as a result of improving glycaemic control (20-40 month follow up) [12]. By contrast, a 24 week long study by Ryan et al [5] showed that improved glycaemic control led to improved working memory, although no improvement in verbal memory was observed. Whilst comparable cognitive tests were used by both Launer et al and Ryan and colleagues, the shorter follow up period and smaller sample size (145

participants vs. over 2000 in the ACCORD-MIND study) of Ryan et al's study were potentially insufficient to account for longer term effects of tighter glycaemic control. These findings suggest that the deficits caused by hyperglycaemia may be irreversible and highlight the importance of very early interventions to reduce the length of exposure to chronically high blood glucose.

Hypoglycaemia has also been shown to adversely affect memory. In healthy adults, induced hypoglycaemia via a hyperinsulinemic glucose clamp has been found to impair working and delayed visual memory [13]. Aung and colleagues [14] reported that DM2 patients who had a self-reported history of severe hypoglycaemia performed significantly worse on age-sensitive neuropsychological tests (Verbal Fluency, the Digit Symbol test and Letter-Number sequencing from the Wechsler Adult Intelligence Scale III and the Trail-Making Test Part B) compared to those who had no history of this condition. The authors derived a general late-life cognitive ability factor from these tests (which they called 'g'), and reported that hypoglycaemia was a contributing factor to cognitive decline, even after pre-morbid intelligence and other confounds were statistically controlled. Despite its apparent detrimental effects, the occurrence of hypoglycaemia in DM2 is not commonly reported, possibly due to patients being unaware of its symptoms when mild hypoglycaemia occurs [15, 16]. Further long term investigation of hypoglycaemia's effects on cognitive performance in DM2 is clearly needed.

In addition to the accelerated cognitive decline observed in DM2, it is also reported that people with DM2 are at greater risk of dementia [2, 17]. This risk is most often attributed to the effects of hyperglycaemia on the brain, although severe episodes of hypoglycaemia may also increase its probability [18]. Further, a combined factor of verbal episodic memory deficits and elevated glycaemia has been found to predict 'pre-dementia', highlighting the complex relationship existing between diabetes, dementia and cognitive function [19]. This may be a consequence of an accumulation of advanced glycation end-products and oxidative stress, which are believed to contribute to neuronal damage in DM2, and are also seen in Alzheimer's disease (AD) [20, 21]. Considering this, research into the damaging effects of type 2 diabetes on brain structure and

function is of critical importance to understanding the extent to which cognitive processes, including memory, are affected.

DM2 and the brain – Global structure

Despite continued research, no clear consensus has emerged regarding the effects that DM2 has on whole brain structure. Some studies suggest that DM2 leads to increased loss of neurons (brain atrophy), a higher incidence of brain infarcts caused by blocked blood vessels in the brain, and white matter hyperintensities (WMHs), all resulting in poor cognitive performance [4, 22]. Considering this, Manschot, Biessels, de Valk, Algra and van der Grond et al [4] used MRI (see Appendix 1) to determine the potential effects of abnormal glucose metabolism on the structural integrity of the brain and cognition. On MRI measures, patients had significantly more infarcts and more severe brain atrophy (cortical and subcortical) than controls, although no specific brain regions were reportedly affected. They also found that individuals with DM2 performed significantly worse on three cognitive measures (including verbal episodic memory) compared to healthy controls, implying hippocampal and temporal gyri specific deficits. However, Christman et al [23] found that there was no difference in grey matter volume, white matter volume or number of WMHs between healthy participants and those with DM2, although those with DM2 had smaller brain to intercranial volumes. This suggests that those with DM2 may experience higher shrinkage of the brain compared to their healthy counterparts. These mixed findings may be due to the differing sample sizes and patient to healthy control ratios. Manschot et al compared 122 DM2 participants with 56 healthy participants; whilst in Christman's study, only 25 DM2 participants were compared to 150 controls.

Whether structural integrity is affected longitudinally and by vascular disease is also of interest. In a three year longitudinal study, van Elderen et al [24] used MRI to investigate the differences in neurodegenerative progression and cognition between healthy controls and DM2 patients aged between 70 - 82 years old. Over the three year period, they noted changes in the number of infarctions, total brain volume changes and WMH volume changes from baseline.

Patients showed significantly more total brain atrophy at follow-up compared to healthy controls, but there were no between-group differences in WMH volume changes or number of infarctions. On tests of cognitive function, their DM2 participants performed worse at baseline on all three tasks (a modified Stroop task and a test of delayed and immediate visual memory recall) than controls. At follow-up, their patients only showed significant decline on the Stroop task and immediate recall compared to controls, with only visual memory scores correlating with total brain atrophy. Tiehuis and colleagues [22] investigated whether vascular disease and DM2 independently affected cognition and brain structure in individuals with arterial disease. Overall, individuals with both DM2 and arterial disease performed worse on tests of attention, memory and visuoperception compared to those with arterial disease alone, even after adjustment for vascular risk factors. DM2 participants had more brain atrophy, white matter lesions and lacunar infarcts. Global and cortical atrophy were significantly negatively associated with an overall composite score of cognition (derived from the three aforementioned domains and executive function test scores) in participants with DM2, both with and without arterial disease, suggesting that DM2 affects cognition irrespective of arterial disease status. In a related study, the authors also found that duration of illness for diabetes contributed to global brain atrophy in those with both DM2 and arterial disease [25], indicating that duration of impaired glucoregulation is also a modifying factor in DM2 cognition. Both van Elderen and colleagues and Tiehuis et al's studies indicate that global brain atrophy in DM2 is correlated with memory decline, but neither speculate how this atrophy affects specific memory processes, such as the encoding, storage or retrieval of memories. By not considering the influence of atrophy on precise mechanisms, they overlook neurocognitive mechanisms which may underpin cognitive impairment in DM2.

The pivotal ACCORD trial's sub-study, Memory in Diabetes (MIND), has suggested that intensive glycaemic therapy (involving the reduction of patient HbA1c levels to less than 6.0%) versus standard glycaemic therapy (HbA1c levels targeted between 7.0-7.9%) through a range of strategies and drug classes does not reduce the overall effects of diabetes on memory [12].

Regardless, the results did indicate that those on the intensive therapy had higher total brain volumes at the end of the trial relative to those on standard therapy, suggesting that the rate of brain atrophy can be reduced with improved glycaemic control. However, in this respect none of the studies above consider whether type 2 diabetes has an adverse effect on specific brain regions critical to cognitive or memory processing, such as the hippocampus. The location of where lesions and infarcts occur should be more precisely measured in the hippocampus to fully consider their impact.

DM2 and the brain – The hippocampus

Research suggests that participants with DM2 have increased hippocampal atrophy compared to health controls [26] and that this is related to hippocampally-mediated deficits in the verbal episodic memory domain (see Appendix 2 for an explanation of the role of the hippocampus in memory) [27]. A recent study by Hayashi et al [28] found that in Japanese older adults (aged over 65), DM2 participants showed more hippocampal and whole brain atrophy than healthy controls. They also found that hippocampal atrophy correlated negatively with cognitive function (as measured using the Mini-Mental State Examination and the Revised Hasegawa Dementia Scale). Reduced hippocampal volume coupled with reports of reduced connectivity to surrounding brain regions [29] may explain cognitive impairment in DM2, although the tests employed by Hayashi et al are not sufficiently sensitive to specific memory deficits. Another study by Yau et al [30] used diffusion tensor imaging (DTI), a type of MRI that allows examination of water molecule diffusion in tissues and white matter, to investigate white matter abnormalities and emotional memory in DM2. They found that patients had impaired emotional memory compared to healthy controls. The DTI results revealed significant white matter abnormalities in DM2 patients, particularly in areas involved in memory and emotion processing (right prefrontal and, left middle and left superior temporal cortices). Although the above studies attempted to couple structural abnormalities in

memory-related brain regions with behavioural evidence, they did not analyse the functional integrity of these regions.

Interestingly, it has been further suggested that there is evidence of sex differences in DM2 hippocampal volume reductions. In the general population, women are found to have larger hippocampi than men [31]. In a study investigating sex effects on hippocampal volume in DM2, Hempel and colleagues [32] found that women had more substantial volume reductions relative to healthy controls than those observed in men. The authors suggested that women with DM2 may therefore suffer more brain complications relative to their male counterparts, despite having better glucose control on average [32]. Yau et al [30] found that there was a trend toward blunted emotional memory facilitation in female diabetic participants but not in males. Therefore, there is robust evidence of an association between hippocampal integrity and cognitive performance in DM2. As the hippocampus appears to be the brain region which is preferentially affected in DM2 [27], the extent of the impact that hippocampal atrophy may have on functional capacity of this brain region, particularly for memory, may be further investigated using functional neuroimaging.

DM2 and functional brain imaging

The majority of neuroimaging studies have sought to determine which structural abnormalities are associated with the cognitive decline observed in DM2. Very few studies to date have employed MRI to uncover the functional bases of memory impairments in DM2 (see Appendix 3). Zhou et al [29] asked DM2 patients and healthy controls to complete a variety of cognitive tests, with the aim of comparing cognitive performance to the resting-state functional connectivity (where the BOLD response is monitored in the absence of the participant performing an explicit task) of the hippocampus. They found that DM2 participants' performance was significantly worse on a number of neuropsychological tests, including the Auditory Verbal Learning Test of verbal episodic memory, relative to healthy controls. This poor performance was associated with poorer glycaemic control as indexed by HbA1c levels. DM2 patients also showed reduced hippocampal connectivity to

surrounding bilateral brain regions including the frontal gyrus, fusiform gyrus and temporal gyrus. These studies suggest that functional networks intimately associated with memory are adversely affected by DM2. These regions underpin memory processes such as face recognition [33] and word retrieval [34]; thus disruption to these networks may contribute to overall memory deficits. Further research should investigate whether there are observable functional differences between healthy individuals and those with DM2, allowing the tailoring of interventions to target the brain regions involved.

Little research has looked at EEG frequencies (see Appendix 4) in DM2 (e.g. [35]), although a number of studies have been carried out in those with type 1 diabetes (DM1) [36]. Further work in the area should use EEG to investigate brain frequencies related to memory, such as the beta and gamma wave frequencies, particularly given that this activity has been found to be decreased in the temporal lobes of those with controlled DM1 [37]. Brismar et al [37] suggested that this decrease in activity may be linked to cognitive decline in DM generally, so future research should address this in those with DM2. Few studies have also looked at functional connectivity (the correlation of neuronal activity between separate distinct sites across the brain) in either DM1 or DM2. Such studies would enable the investigation of connectivity between brain regions associated with memory processing such as the frontal gyrus and hippocampus, consolidating research already done in the area using fMRI [29].

Some studies have indicated that patients with DM2 have a longer P300 latency [35, 38, 39], although others have found no differences compared to healthy controls [40]. Importantly, strict glycaemic control has been shown to lead to improvements in P300 latency and potential memory enhancement [35, 39]. Cooray et al [35] used EEG to investigate the effects of glycaemic control on cognitive decline. They compared the behavioural cognitive performance and auditory ERPs of i) DM2 patients on their regular treatment, ii) DM2 patients on an intensified glycaemic control regime (comprising of optimised drug treatment, frequent daily blood glucose monitoring and instructions on improving diet and exercise levels) and iii) healthy controls. Initially, individuals with DM2

performed significantly worse on tests of verbal fluency and visuospatial ability relative to healthy controls. Participants were presented with an auditory ERP task, whereby they pressed a response key in the left hand if they heard a low pitch tone or pressed a response key in the right hand if they heard a high pitch tone. The authors observed a lower N100 amplitude (indexing responses to unpredictable auditory stimuli [41]) and longer P300 latency in DM2 patients. A lower EEG beta band resting activity (which is associated with alertness) was also observed, suggesting that DM2 patients were less alert and attentive to the task. Those DM2 patients who then underwent intensified glycaemic control performed significantly better on the visuospatial and semantic memory tasks at re-test. DM2 participants also demonstrated a significant increase in beta band connectivity, and the mean ERP amplitudes of the N100 and P300 components were significantly closer to healthy controls ($p < .001$) than those patients on regular treatment. The improvements in cognitive ability and associated neurocognitive ERPs show the importance of glycaemic monitoring and control for regulating cognitive performance in DM2. This study further highlights the importance of putting interventions in place to attenuate fluctuations in glycaemic control. However, the ERPs considered here are not related to more sensitive markers of memory retrieval (i.e. the recollection left-parietal and the familiarity old/new effect) [42]. These components have been used elsewhere to disentangle the memory impairments in normal ageing [43]

Future directions and conclusions

As seen above, neuroimaging can be used to explore the effects of physiological mechanisms associated with DM2 on both brain structure and function, although evidence on functional deficits in DM2 is sparse. fMRI, EEG and ERP techniques have allowed the identification and investigation of specific memory impairments and deficits in other cognitive domains, such as information processing and executive functions in DM2. A global effect on cognition could potentially be identified through these methodologies to further our understanding of the effects of DM2. EEG frequency and connectivity studies have furthered our understanding of the neurocognitive

mechanisms underpinning cognitive deficits in DM1; therefore future work in DM2 should follow a similar strategy to enhance current knowledge of deficits both memory and global cognition.

Neuroimaging has had an impact on knowledge above and beyond that of behavioural research in the area by allowing researchers to investigate the brain's structural integrity and its influence on DM2 cognition. Both MRI (good spatial resolution) and ERPs (good temporal resolution) can be used to determine more precisely the neurocognitive mechanisms that underlie memory impairments. These techniques can potentially be used to determine whether deficits are predominantly explained by specific impairments in the encoding, storage or retrieval of memories, or whether memory deficits are mediated by compromised structural integrity and functioning of the hippocampus. By using these neuroimaging techniques to their full potential, there is scope to develop targeted interventions that can help individuals with DM2 compensate for memory problems they may encounter. Identification of the precise mechanisms that underlie cognitive complications in this condition may provide more specific avenues for intervention, including capitalisation on those aspects of memory functioning which remain intact. Importantly, these laboratory investigations will have implications for research on 'real world' memory and the cognitive difficulties in the everyday lives for those with DM2, particularly when considering important tasks such as taking medications or remembering to attend medical appointments.

Abbreviations

AD	Alzheimer's Disease
BOLD response	Blood oxygen level dependent response
DM2	Type 2 Diabetes
DTI	Diffusion Tensor Imaging
EEG	Electroencephalogram
ERP	Event-related Potential
fMRI	Functional Magnetic Resonance Imaging
HPA axis	Hypothalamic Pituitary Adrenal axis
MRI	Magnetic Resonance Imaging
WMH	White Matter Hypertensities

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Appendices

Appendix 1. *Structural brain imaging* has allowed researchers to visualise structures and abnormalities (e.g. lesions, tumours etc) that may occur within the brain. Magnetic resonance imaging (MRI) is a prominent tool frequently used in both structural and functional imaging. In MRI, signals from water molecule protons become differentially aligned by the large magnet of an MRI scanner, subsequently allows the visualisation of the brain. It has been used to investigate changes in brain structure resulting from diabetes-related complications which may mediate the physiological mechanisms mentioned above, as well as functional connectivity between the hippocampus and surrounding brain regions related to memory [29]. As such, many structural imaging studies have investigated the effects of DM2 on the brain as a whole, as opposed to specific brain regions.

Appendix 2. A proportion of neuroimaging research has focussed on trying to identify specific regions of atrophy within the brain that may explain the specific cognitive deficits exhibited by individuals with DM2. In particular, atrophy in the hippocampus and temporal lobes have frequently been associated with impaired memory, even in 'healthy' older adults with impaired glucose tolerance [44]. The hippocampus supports both recollection (remembering an item and the context it was last seen in) and familiarity (remembering an item but not recalling details for when it was previously encountered), mechanisms considered integral to memory processing [45].

Appendix 3. Functional neuroimaging allows researchers to investigate regional brain activity during specific cognitive tasks. This is commonly measured through imaging changes in the blood oxygen level dependent (BOLD) haemodynamic response in MRI, or via electrical activity through the scalp using EEG associated with direct activation of neural populations.

Appendix 4. EEG is a neuroimaging method used to investigate cognitive function by measuring electrical brain activity through the scalp surface. This methodology offers excellent temporal resolution (milliseconds), allowing the measurement of brain frequencies and responses to particular events (known as event related potentials [ERPs]). This has enabled researchers to track cognitive processes such as unconscious versus conscious aspects of memory or states of alertness. One particular ERP component affected by DM2 is the P300. This component is a positive peak in the EEG waveform, detectable from approximately 300ms post stimulus onset, often split into two separate subcomponents; the P3a associated with executive function and orientation of attention and the P3b associated with memory updating and formation of memory representations [46].