Title

Meta-analyses of structural regional cerebral effects in type 1 and type 2 diabetes

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Abstract

Diabetes is associated with macrovascular and microvascular complications and is a major risk factor for neurological and psychiatric disorders, such as dementia and depression. Type 1 diabetes (T1DM) and type 2 diabetes (T2DM) have distinct etiologies and pathophysiological effects while sharing a common endpoint of persistent hyperglycemia. Neuroimaging studies in T1DM have revealed reductions in numerous regions, including the parahippocampal and occipital regions, while in T2DM there have been numerous reports of hippocampal atrophy. This meta-analysis aimed to identify consistent regional abnormalities in cerebral structures in T1DM and T2DM respectively, and also to examine the impact of potential confounds, including age, depression and vascular risk factors. Neuroimaging studies of both voxel-based morphometry (VBM) data and volumetric data were included. Ten T1DM studies (n=613 patients) and 23 T2DM studies (n=1364 patients) fulfilled inclusion criteria. The T1DM meta-analysis revealed reduced bilateral thalamus grey matter density in adults. The T2DM meta-analysis revealed reduced global brain volume and regional atrophy in the hippocampi, basal ganglia, orbitofrontal and occipital lobes. Moreover, hippocampal atrophy in T2DM was not modified by hypertension, although there were more marked reductions in younger patients relative to healthy controls. In conclusion, T1DM and T2DM demonstrated distinct cerebral effects with generalised and specific target areas of grey matter reduction. Thalamic atrophy in T1DM may be a substrate of associated cognitive deficits. In T2DM, global cerebral atrophy may reflect atherosclerotic factors, while hippocampal atrophy was an independent effect providing a potential common neuropathological aetiology for the comorbidity of T2DM with dementia and depression.

1. INTRODUCTION

Diabetes is a multi-system disease characterised by persistent hyperglycemia associated with numerous macrovascular complications, such as cardiovascular and cerebrovascular disease, as well as microvascular complications, including retinopathy, nephropathy and neuropathy. Diabetes has emerged as a major risk factor for numerous conditions affecting the central nervous system. Up to 20% of adults with diabetes meet criteria for major depression (Ali et al. 2006), and diabetes doubles the risk of Alzheimer's disease and all-cause dementia (Jorm 2000).

Diabetes is currently subdivided into two subtypes which share a common end-point of persistent hyperglycemia. However, type 1 diabetes (T1DM) and type 2 diabetes (T2DM) have different etiologies. T1DM results from autoimmune destruction of islet beta-cells with a typical onset in childhood and young adulthood. T2DM usually results from increasing resistance to the end-organ actions of insulin and progressive impairment of insulin secretion, and its end effects often occur with other cardiovascular risk factors, such as hypertension, dyslipidemia and obesity (Stamler et al. 1993).

Altered cerebral metabolism has been observed in T1DM in children (Sarac et al. 2007). T1DM in adults has been associated with neurocognitive deficits, such as impaired attention and information processing (Brands et al. 2005), and corresponding reductions in cortical and subcortical regions, including occipital and inferior frontal (Wessels et al. 2006), thalamus and parahippocampal regions (Northam et al. 2009). In T2DM, decreases in whole brain volume (Espeland et al. 2013) as well as in regional volumes, namely in the hippocampus and amygdala (den Heijer et al. 2003), anterior cingulate (Kumar et al. 2008) and cerebellum (Manor et al. 2012) have been observed. Findings have been mixed in part due to variability in method of analysis, some studies using voxel-based morphometry (Musen et al. 2006) with others using volumetric analysis (Lobnig et al. 2005), and some studies have limited their analyses to specific regions of interest (Anan et al. 2010; Kamiyama et al. 2010).

In order to investigate the regional cerebral correlates of T1DM and T2DM, we performed a meta-analysis of studies of grey matter effects including studies of both VBM and volumetric measures. Our aim was to identify the consistent regional abnormalities in T1DM and T2DM

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and to examine the effects of the potential confounds of depression, hypertension, hyperlipidemia, glycemic control, age and gender. We hypothesised that grey matter changes in T2DM would demonstrate strong parallels with the deficits observed in depression and dementia, namely hippocampal atrophy (Cole et al. 2011), whilst other regional abnormalities would be observed in T1DM.

2. MATERIALS AND METHODS

2.1. Literature search

The meta-analyses followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We systematically searched Web of Science and MEDLINE for original articles published before May 2013 using the following search strategy: (diabetes OR diabetic) AND (morphometry OR voxel-based OR voxelwise OR VBM OR volumetric OR 'gray matter' OR 'grey matter' OR 'brain volume' OR 'brain volumes' OR 'cortical atrophy' OR 'brain atrophy' OR 'subcortical atrophy' OR MR OR MRI OR 'magnetic resonance'). Studies using animals, other imaging modalities, and patients with major psychiatric comorbidity (e.g. psychosis, alcoholism) or previous cerebrovascular disease were excluded. Titles were reviewed to exclude studies not meeting the inclusion criteria, and remaining abstracts were examined. From abstracts meeting inclusion criteria, full-text articles were reviewed, and relevant studies carried forward for data extraction. Reference lists of included papers were checked for additional publications, and both published and unpublished articles were included.

2.2. Criteria for inclusion in analysis

Inclusion criteria were: 1) volumetric and/or voxel-based morphometry data on grey matter structure in either T1DM or T2DM; 2) at least one direct structural or longitudinal comparison was made between patients and controls; 3) MRI imaging was used with voxel-based analysis or volumetric data produced using a validated manual- or automatic segmentation method; and 4) whole-brain and/or region of interest (ROI) analysis was produced. Studies were excluded if they met any of the following criteria: 1) patients had a diagnosis of insulin resistance; 2) study did not differentiate T1DM from T2DM; 3) only white matter data were presented; 4) fewer than 10 individuals were included or fewer than 5

subjects in either group; 5) study included patients with dementia only; 6) study re-analysed previously published data; 7) study was a review article without original data; or 8) not published in English (Figure 1).

2.3. Data extraction

The following data were extracted for all relevant studies: authors; year of publication; sample size; age (mean + standard deviation (SD)); type of diabetes; MRI modality and method of analysis used.

We identified the following possible confounders: duration of diabetes (mean + SD); HbA1c percentage at time of study (mean + SD), converted to International Federation of Clinical Chemistry-standardised concentrations (mmol/mol); hypertension; hyperlipidemia; previous stroke; dementia; insulin therapy; and correction for intracranial volume. Covariate analysis was performed when there were at least 5 independent studies with complete data for a particular brain region. If covariate analysis was not possible, stratified analysis was performed (e.g. analysing studies with children and adult participants separately). For any data reported as mean +/- standard error, the latter was converted to its SD for inclusion in the meta-analysis. For prospective studies, baseline measures were also included in the meta-analysis when available.

Studies presenting overlapping or identical samples were identified, and only the study presenting the largest number of subjects retained. If there was possible overlap but different results were presented, for example hippocampus presented in one study and frontal lobe in the other, all data were included. The following 9 studies were assimilated into 4 studies because of potential sample overlap: i) Brundel et al. 2010; de Bresser et al. 2010 and Jongen et al. 2007; ii) Anan et al. 2010 and Anan et al. 2011; iii) Manor et al. 2012 and Novak et al. 2011; iv) Hershey et al. 2010 and Perantie et al. 2011.

2.4. Volumetric meta-analysis

Grey matter volumetric measurements of global (whole brain) or regional volumes were included which were reported by at least 2 studies. Authors were contacted for studies in which the reported measurements were unclear.

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DerSimonian-Laird random-effects meta-analysis was used (DerSimonian and Laird 1986). In this method, the standard errors of the study-specific estimates are adjusted to incorporate a measure of heterogeneity observed in different studies. The amount of variation, and hence the adjustment carried out, is estimated from the intervention effects and standard errors of included studies. R statistical software was used to produce an effect size estimate (Hedge's g) for each region analysed (standardised mean difference for continuous variables), 95% confidence interval, and z-value and p-value (Viechtbauer 2010). The heterogeneity quantifier I^2 was produced for each area of interest (Higgins et al. 2003).

2.5. Voxel-based morphometry meta-analysis

Voxel-based morphometry (VBM) is a fully-automated and standardised method of determining tissue-type probabilities (Ashburner and Friston, 2000), and we performed a meta-analysis to produce a whole-brain summary map based on VBM effect sizes. The following data were extracted: normalization template (such as MNI or Talairach); x/y/z coordinates; area examined (whether whole brain or region of interest); statistic used to report the findings (if p-values, whether uncorrected or corrected and the type of correction used); effect sizes; and the size of the smoothing kernel used. If the statistical threshold was not reported by a study, the smallest effect size of significant findings was used as a conservative estimate. For region of interest analyses or when the coordinates were not specified, automated anatomical labels (AAL) were used to record the relevant area (Tzourio-Mazoyer et al. 2002). Where appropriate, we duplicated the result to account for more than one AAL label.

Parametric coordinate-based meta-analysis (PCM) was used to analyse the VBM data (Costafreda 2012). PCM is a method that can incorporate positive, negative and sub-threshold statistical findings from VBM studies, themselves with different statistical thresholds, to generate a valid pooled effect size summary. A finding can be incorporated into PCM if sufficient information is reported to compute the effect size associated with the finding, and PCM employs a spatial kernel to account for the spatial uncertainty in location. If a study reported both whole-brain and ROI contrasts, the most precise measurement available (either an exact measurement for a significant finding or most conservative threshold for a negative

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result) is used in the summary map for that study. PCM corrects for multiple comparisons using the false discovery rate correction (q = 0.05).

Each significant triplet of spatial coordinates is assigned to the corresponding location in MNI space, and this location receives the effect size reported, either as exact value or significant interval (not crossing zero). Two maps are created, reflecting the lower and upper bounds of these intervals. After convolution with the kernel, the outcome is a brain map for study i, in which either a significant measurement (if the location is located within ρ of a significant finding) or a non-significant measurement (determined by the statistical threshold) is assigned to each location within the field of view. Outside of this, the measurement is not defined. The non-significant measurement will be left- or interval-censored containing zero, bounded by the threshold $t_{i,}$. If the threshold is not stated in the paper and cannot be computed or approximated, the significance of the smallest significant finding is used to estimate t_i, thereby maximising the width of the non-significance interval and producing a conservative estimate. This method demonstrates high agreement between its estimates and those obtained from the meta-analysis of unthresholded manual volumetric measurements, and further details on PCM methods have been published (Costafreda, 2012).

3. RESULTS

In T1DM, 10 studies (n = 613 T1DM patients, mean age 26.6 years; n = 375 healthy controls, mean age 25.8 years) consisting of 6 VBM (n = 453 patients, n = 286 controls) and 4 volumetric (n = 160 pts, n = 89 controls) studies were eligible for inclusion (Table 1). In T2DM, 23 studies (n = 1364 T2DM patients, mean age 63.2 years; n = 3433 healthy controls, mean age 60.5 years), consisting of 6 VBM (n = 216 pts, n = 202 controls) and 17 volumetric studies (n = 1148 patients, n = 3231 controls) were included (Table 2).

Average duration of diabetes was 14.5 years for T1DM and 10.3 years for T2DM, and average HbA1c was 8.2% (66 mmol/mol) for T1DM (Table 1) and 7.6% (60 mmol/mol) for T2DM (Table 2), as a proxy measure of glycemic control. Additional potential confounders of depression, dementia, stroke, hypertension, hyperlipdemia and correction for intracranial volume are presented in Supplementary Tables 1 and 2.

3.1. Type 1 diabetes

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In the volumetric meta-analysis, there were no significant differences between in total brain volume, total grey matter volume, or hippocampal volume (all p > 0.1), and these results are published as supplementary material (Supplementary Figure 1, Supplementary Table 3).

In the VBM meta-analysis, significant reductions were observed in both the left thalamus (cluster size 5768 mm^3, subregion volume 5112mm^3, MNI coordinates (-14, -22, 0), z=4.46, p<0.05 FDR corrected) and right thalamus (cluster size 5768 mm^3, subregion volume 612 mm^3, MNI coordinates (4, -16, 0), z=4.46, p<0.005 FDR corrected) as compared to controls (Figure 2). Stratification by age revealed significant thalamic reductions in the aggregation of studies which included adults (Musen et al. 2006; Northam et al. 2009; Wessels et al. 2006), but no differences in children (Perantie et al. 2007; Perantie et al. 2011). No other regions showed any significant differences between T1DM and healthy controls.

3.2. Type 2 diabetes

The volumetric meta-analysis demonstrated significant global reductions in total brain volume (Z=-2.77, p=0.006), brain parenchymal fraction (Z=-7.77, p<0.001) and grey matter volume (Z=-4.75, p<0.001) (Table 3, Supplementary Figures 2-3). Regional reductions were revealed in orbitofrontal cortex grey matter (Table 3, Z=-3.29,p=0.001), the hippocampus (Figure 3, Z=-3.67,p=0.0002) and basal ganglia (Table 3, Z=-2.61,p=0.009). Reductions in frontal and temporal volumes approached statistical significance (p=0.057 and p=0.066, respectively) (Supplementary Figure 4). There were no significant differences in anterior cingulate, superior temporal and parietal regions (Table 3).

The VBM meta-analysis revealed significant reductions in both the left hippocampus (cluster size 7224 mm^3, subregion volume 7224 mm^3, MNI coordinates (-32, -6, -26), z=2.67, p=0.0076) and right hippocampus (cluster size 7296 mm^3, subregion volume 7296 mm^3, MNI coordinates (26, -6, -26), z=2.67, p=0.0076) compared to healthy controls (Figure 4).

We also examined potential longitudinal changes, which was possible for total brain volume from 2 studies (n = 113 patients, mean age 65.9 years; n=668 controls, mean age 78.1 years) (de Bresser et al. 2010; Espeland et al. 2013). Accelerated brain atrophy was evident in older T2DM patients relative to age-matched healthy controls (Hedges' g = -0.25 95% CI (-0.49;-0.02); z=2.16, p=0.03) with a follow-up period of 4.7 and 4.1 years respectively.

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3.3. Modifier analysis

Modifier analysis was only performed if there were at least 5 studies with complete data for a particular region. Reductions in total brain volume and the hippocampus in T2DM were robust to adjustment by age (Table 3), and age was a significant modifier of the differences between patients and controls in hippocampal volume, with studies that included younger patients showing more marked reductions between patients and controls than those including older participants (modifier effect $Z = 6.2$, $p<0.001$).

Hypertension was associated with more pronounced differences in frontal volumes between T2DM patients and controls: studies where a higher proportion of patients with T2DM had comorbid hypertension reported smaller frontal volume in T2DM relative to controls (modifier $Z = -2.51$, $p=0.012$). There were no significant effects of gender or age on frontal reductions. For total grey matter volume, hypertension as a modifier of the differences between patients and controls approached statistical significance (modifier $Z=-1.89$, $p=0.058$), whereas age, gender or HbA1c did not modify these differences. For hippocampal volume, neither hypertension nor glycemic control (using HbA1c as a proxy measure) modified the differences between patients and controls, though again data were limited and between-study differences in HbA1c relatively small.

Where possible, the effect of depression on results was analysed by estimating differences within each study between both groups of patients. There was no evidence that depression was associated with differences in anterior cingulate or orbitofrontal volumes, although only 2 studies examined these areas, and no data were available for hippocampal volume. Due to the limited number of studies, modifier analysis was not performed in T1DM studies or to examine the effects of hyperlipidemia.

4. DISCUSSION

Our meta-analysis of the structural brain changes associated with T1DM and T2DM demonstrated distinct effects within the conditions with generalised and specific target areas of grey matter reduction. T1DM was associated with significant bilateral reductions that were limited to the thalamus in adults with T1DM. In contrast, T2DM was associated with

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widespread global cerebral atrophy, which declined more rapidly over time compared to healthy controls, as well as regional atrophy, particularly in the hippocampus, basal ganglia, orbitofrontal and occipital lobes. While hypertension modified the global cerebral effects of diabetes, indicating a potential atherosclerotic contribution, there was no significant modifier effect of hypertension on hippocampal atrophy, which may provide a common neural pathology for the high comorbidity of T2DM with dementia as well as depression.

4.1. Type 1 diabetes

The VBM meta-analysis revealed significantly lower grey matter density in the right thalamus in T1DM. The significant reductions in thalamus were not seen when analysing childhood studies only. In support, blunted thalamic blood flow has been reported in T1DM (Mangia et al. 2012). There is growing interest into the neuropsychological effects of T1DM in both children and adults, with decrements found in IQ, attention and higher-order executive function (Gaudieri et al. 2008; Naguib et al. 2009). The area of the right thalamus identified in our meta-analysis is thought to have prominent projections to the prefrontal cortex with no motor connections (Oxford Thalamic Connectivity Atlas 2003), so could potentially be a substrate of associated cognitive deficits. Insulin receptor expression is particularly rich in the anterior thalamic and hypothalamic nuclei of rat brains (Bondy et al. 1992), identifying the thalamus as an area of potential vulnerability to damage in T1DM.

The effects of T1DM on cognitive impairment have been linked both with prolonged exposure to hyperglycemia (Musen et al. 2006) and with repeated episodes of hypoglycemia, though this has been disputed (DCCT et al. 2007). In our meta-analysis, the effects of previous hypoglycemia and hyperglycemia were mixed (Musen et al. 2006; Perantie et al. 2011; Aye et al. 2011), but there were insufficient data to test either exposure quantitatively (Supplementary Table 1). .

Some authors have highlighted parallels between the cerebral correlates of T1DM and those of depression, advancing this as evidence for shared biological mechanisms between the two conditions (Korczak et al. 2011). Our meta-analysis, however, suggests that this conclusion is not supported by the available grey matter studies of T1DM and, indeed, that distinct cerebral effects may be observed.

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4.2. Type 2 diabetes

T2DM patients have a 39% increased risk of Alzheimer's disease and a 47% increased risk of all-cause dementia (Lu et al. 2009). Our meta-analysis revealed global cerebral atrophy and implicates the hippocampus as a target of T2DM pathology in the brain. Hippocampal atrophy was demonstrated at high significance and survived covarying for hypertension, making it unlikely that hippocampal atrophy is the result only of vascular risk factors and atherosclerosis. Furthermore, the difference in hippocampal volume was even more marked for younger patients. This probably reflects the increased contribution of factors other than T2DM leading to hippocampal atrophy in older patients, and thereby strengthens the association of hippocampal atrophy with T2DM. In rat models, it has been demonstrated that insulin provides significant neurotrophic support to the hippocampus, which may be impaired in the diabetic brain (Balakrishnan 2010).

Our findings also showed lower volumes of subcortical structures in T2DM compared to healthy controls. In early Alzheimer's disease, amyloid deposits have been found in the striatum (Klunk et al. 2007), while Alzheimer's disease is associated with reduced putamen and thalamic volumes (de Jong et al. 2008). As the basal nuclei and thalamus are involved with emotional, motivational and cognitive abilities (Herrero et al. 2002), the shared finding of reduced subcortical volume in Alzheimer's disease and in T2DM could provide further insight into their relationship. In our meta-analysis, only five studies did not exclude participants with dementia and one of these studies found that covarying for dementia did not modify the significant difference between T2DM and controls (Korf et al. 2006).

As well as dementia, there is a well established bidirectional link between T2DM and depression (Ali et al. 2006; Mezuk et al. 2008). Reduced hippocampal volume has been consistently observed in major depression (Cole et al. 2011; Videbech and Ravnkilde 2004), therefore our finding of reduced hippocampal volume in T2DM may implicate a common pathophysiology. Deficiency of brain derived neurotrophic factor (BDNF) has been linked both to depression and T2DM (Karege et al. 2002; Fujinami et al. 2008), potentially via decrements in hippocampal function (Egan et al. 2003). Unfortunately, in our meta-analysis there were insufficient data to examine whether the interaction between depression and T2DM had a greater effect on hippocampal volume than T2DM alone.

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Both diabetes and depression are associated with activation of the innate inflammatory response (Dowlati et al. 2010; Pickup and Crook 1998), and patients with depression and T2DM have been shown to have higher levels of inflammatory markers than patients with T2DM alone (Laake et al. 2014). Depressed subjects have significantly higher concentrations of tumour necrosis factor-α and interleukin-6 (IL-6) (Dowlati et al. 2010), and high IL-6 levels in depression are associated with reduced hippocampal volumes (Frodl et al. 2012). In addition, both depression and diabetes are also associated with overactivation of the hypothalamic-pituitary-adrenal (HPA) axis (Stetler et al. 2011). Dysregulation of the HPA axis has been observed in patients who experienced childhood stress/adversity, and such patients are at increased risk of developing both depression and incident diabetes in adult life (Colman et al. 2014; Scott et al. 2011). In the brain, structural consequences of early stress include attenuated development of the left neocortex and hippocampus, which have a high density of glucocorticoid receptors (Teicher et al. 2003), while excess cortisol has been shown to hinder hippocampal neurogenesis (Elder et al. 2006). It is possible, therefore, that overactivation of the innate inflammatory response and/or HPA axis may provide a common link between both diabetes and depression and hippocampal atrophy.

Another finding in our meta-analysis was reduced orbitofrontal cortex grey matter in T2DM. This area has been implicated in the regulation and modulation of cognition and mood (Ballmaier et al. 2004), and as a predictor of clinical outcome in depression (Fu et al. 2013), pointing to a potential link between T2DM and associated cognitive impairment as well as depressive symptomatology.

Although the relationship between diabetes and depression and dementia individually is well established, these associations should not be considered in isolation. In T2DM, depression doubles the risk of incident dementia over five years (Katon et al. 2012). The risk of dementia was even more marked for younger patients, while cohort studies of T2DM have found that patients with depression are more likely to be younger (Twist et al. 2013). It is possible, therefore, that younger patients with T2DM – who demonstrated more marked hippocampal atrophy relative to older patients in our meta-analysis – are more vulnerable to the development of psychiatric complications such as depression and dementia, and/or to their detrimental effects on grey matter structure. The temporal relationship of these associations will require longitudinal study, and our meta-analysis identifies the relationship between

T2DM and depression as a major gap in the neuroimaging literature which requires further exploration.

4.3. Possible cellular mechanisms

Several molecular mechanisms have been proposed to explain the regional cerebral effects of diabetes, including cerebral capillary basement membrane thickening, amyloid angiopathy and increased rate of brain infarcts (Biessels et al. 2006). Hyperglycaemia decreases vasodilatation by decreased expression of endothelial nitric oxide synthase, which in turn decreases cerebral blood flow (Tesfomariam et al. 1991; Williams et al. 1998). Impaired insulin signalling and hyperglycaemia cause increased expression and activation of NF-κB, which is a key player in the inflammatory cascade and a modulator of apoptosis (Sima et al. 2009). Chronic hyperglycemia is associated with increased advanced glycation end products, which may enhance inflammatory processes and oxidative stress in the cerebral vasculature (Brownlee 1995). The latter can also contribute to amyloid deposition and tau phosphorylation (Necula et al. 2004), reminiscent of the pathogenesis of Alzheimer's disease. Some authors have highlighted diminished O-linked N-acetylglucosamine glycosylation (O-GlcNAcylation) as a molecular mechanism linking diabetes and Alzheimer's disease. A rat model using stroptozotocin showed down-regulation of O-GlcNAcylation and impaired insulin signalling (Deng et al. 2009). As decreased O-GlcNAcylation is found in Alzheimer's disease and is inversely related to the phosphorylation of tau (Liu et al. 2009), subsequent hyperphosphorylation of tau could lead to pathology associated with Alzheimer's disease.

4.4. Limitations

Our study was limited by a lack of data for many brain areas, in particular for T1DM. Where study numbers were particularly limited, the findings should be treated with caution. Although the lack of a modifying effect of hypertension and more marked differences seen in younger patients lend robustness to the hippocampal findings in T2DM, the greater number of studies examining the hippocampus increases the likelihood of positive findings compared to other brain areas. Lack of data limited the amount of covariate analysis possible, meaning the effect of other confounders on our findings cannot be excluded. A very small number of studies examined patients with potentially confounding disease processes, such as heart failure and arterial disease, though studies examining previous stroke were excluded

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altogether. Although various hypotheses were examined by the included studies, the vast majority examined the general population with T1DM or T2DM.

Our analysis was limited to grey matter changes, thereby not including the large amount of research on white matter changes in T2DM, which would also benefit from consolidation in meta-analysis. As with any meta-analysis, there is heterogeneity in the study populations and methods, for example with different MRI scanners and different segmentation techniques. The largely cross-sectional nature of our analysis makes it difficult to draw firm conclusions about the temporal relationship between diabetes and associated psychiatric conditions. However, by performing two separate meta-analyses, we were able to include 33 suitable studies in the analysis and, through PCM meta-analysis, to include negative results, a feature not possible with some other VBM analysis techniques.

4.5. Conclusions

Diabetes is associated with global cerebral deficits as well as discrete regional cortical and subcortical atrophy. T1DM was associated with lower VBM signal in the thalamus bilaterally, which may provide insight into associated cognitive deficits. T2DM was associated with atrophy in numerous brain areas but most strikingly in hippocampus, a potential link for its high comorbidity and risk for both depression and dementia. The mechanisms behind this may include inflammatory processes, oxidative stress and apoptosis as a result of aberrant insulin signalling. Further research is needed to understand these changes, and longitudinal research into the factors leading to grey matter loss in diabetes and its relationship with other psychiatric conditions is required.

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CONFLICT OF INTEREST

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None declared

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FIGURE CAPTIONS

Fig. 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of search strategy

Fig. 2

VBM meta-analysis map of T1DM (axial, sagittal and transverse cerebral views are presented, overlaid on MNI template). Red areas are statistically significant results (P<0.05 FDR corrected). Significant reductions were found in left thalamus (MNI coordinates (-14, -22, 0), z=4.46) and right thalamus (MNI coordinates (4, -16, 0), z=4.46) in T1DM compared to controls

Fig. 3

Forest plot of hippocampal volume in T2DM studies. Significant reduction in T2DM compared to controls

Fig. 4

VBM meta-analysis map of T2DM (axial, sagittal and transverse cerebral views are presented, overlaid on MNI template). Red areas are statistically significant results (P<0.05 FDR corrected). Significant reductions were found in left hippocampus (MNI coordinates (-32, -6, -26), z=2.67) and right hippocampus (MNI coordinates (26, -6, -26), z=2.67) in T2DM compared to controls

Supplementary Fig. 1

Forest plot of hippocampal volume in T1DM studies. Non-significant reduction found in T1DM compared to controls

Supplementary Fig. 2

Forest plots of total brain volume.   Non-significant reduction found in T1DM compared to controls (left) and significant reduction in T2DM compared to controls (right)

Supplementary Fig. 3

Forest plots of total grey matter volume. Non-significant reduction found in T1DM compared to controls (left) and significant reduction in T2DM compared to controls (right)

Supplementary Fig. 4

Forest plot of total frontal volume. Non-significant reduction found in T2DM compared to controls

Figures

Figure 1

Flow diagram with the following content:

Identification

Records identified through database searching (n = 1402)

Additional records identified through other sources (n = 1)

Screening

Records screened (n = 1403)

Records excluded after titles examined (n = 1282)

Abstracts screened (n = 121)

Records excluded after abstracts reviewed with reasons (n = 63):
-Not relevant (n=15)
-Review article (n=12)
-Only 1 individual in diabetic group (n=1)
-Insulin resistance only (n=3)
-Functional imaging only (n=7)
-No control group (n=10)
-Duplicate results from other study (n=2)
-No imaging (n=1)
-White matter only (n=2)
-Conference (n=2)
-Letter (n=3)
-Type 1 and 2 diabetes combined (n=4)
-Measurements not comparable with other studies (n=1)

Eligibility

Full-text articles excluded with reasons (n = 25):
-Not volumetric or VBM (n=2)
-Not accessible (n=2)
-Type 1 and 2 diabetes combined (n=6)
-Measurements not comparable with other studies (n=9)
-Review article (n=1)
-Functional imaging only (n=1)
-Duplicate results from other studies (n=2)
-Conducted in purely dementia population (n=1)
-No control group (n=1)

Full-text articles assessed for eligibility (n = 58)

Included

Studies included in qualitative synthesis (n = 33; 10 studies on type 1 diabetes, 23 studies on type 2 diabetes)

Studies assimilated into other studies using same population but presenting different data (n=5)

Studies included in final meta-analysis (n=28)

Figure 2

Figure 3

	Hedges' g [95% CI]
DenHeijer 2003	−0.34 [−0.66 , −0.02]
Gold 2007	−1.34 [−1.98 , −0.70]
Korf 2006	−0.07 [−0.26 , 0.13]
Hempel 2012	−1.30 [−1.97 , −0.64]
DeBresser 2010	−0.81 [−1.27 , −0.35]
Bruehl 2010	−0.86 [−1.62 , −0.10]
Musen 2012	−2.38 [−3.50 , −1.26]
RE Model	−0.88 [−1.36 , −0.41]

Decrease in Patients   Decrease in Controls

−4.23   −2.96   −1.69   −0.42   0.85
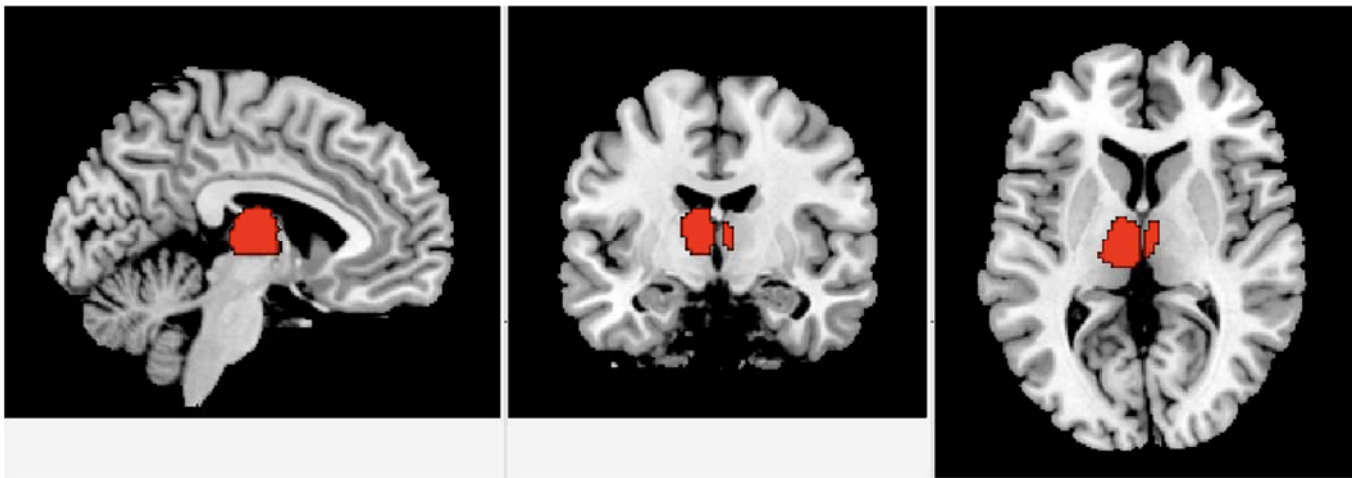
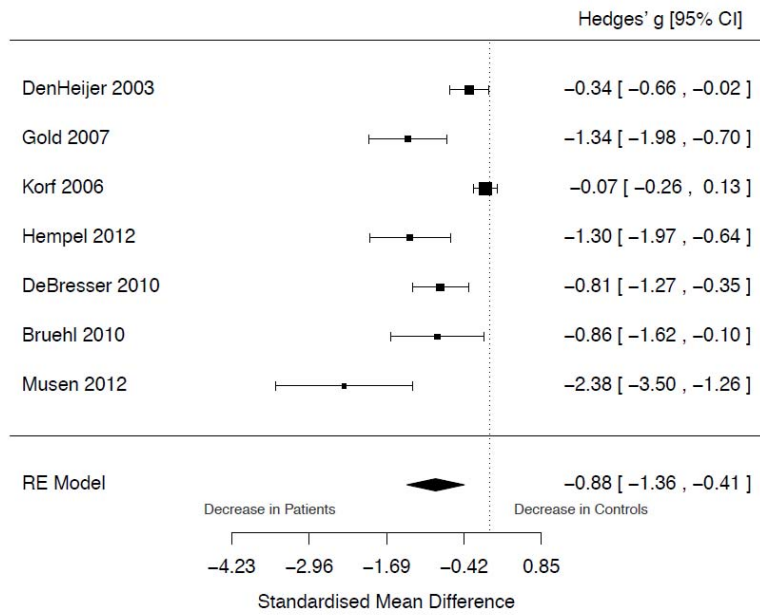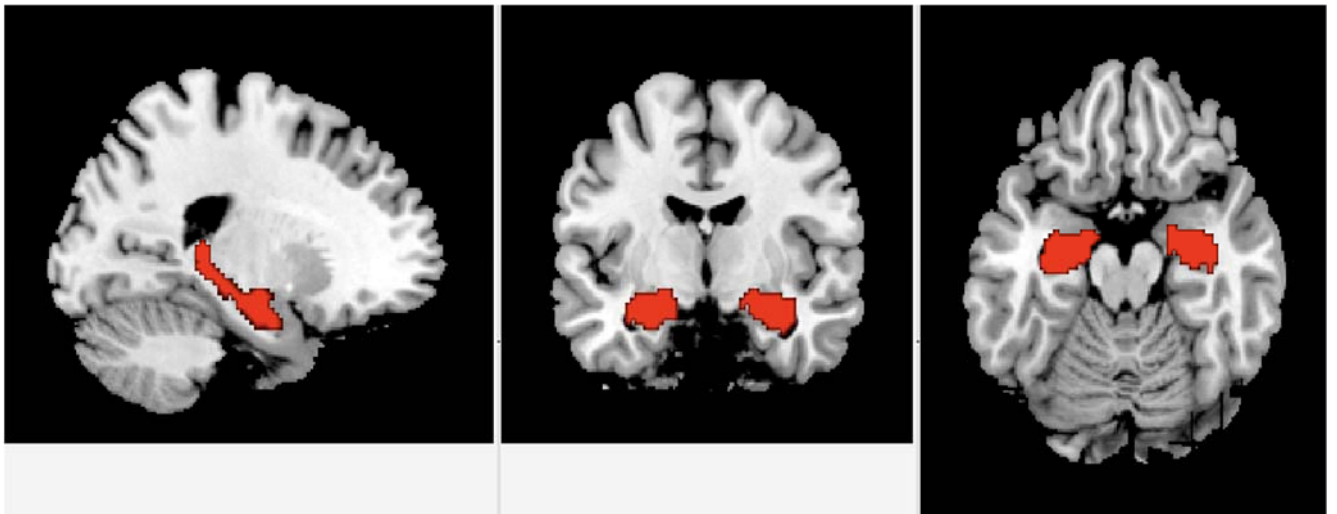Standardised Mean Difference

Figure 4

Table 1: T1DM demographic and neuroimaging characteristics

Paper	Year	Number of patients (male)	Number of controls (male)	Mean age of patients	Mean age of controls	Diabetes duration	HbA1c (%)	Number receiving insulin therapy	MRI magnet strength	Image processing technique
Aye	2011	27 (13)	18 (11)	7 ± 1.4	7.2 ± 1.6	3.6 ± 1.9	7.6 ± 1.0	27	1.5T	Manual segmentation
Hershey	2010	95 (52)	49 (0)	12.4 ± 2.8	12.4 ± 2.7	5.4 ± 2.8	8.3 ± 1.0	95	1.5T	Automated segmentation
Lobnig	2005	13 (9)	13 (9)	41.3 ± 1.3	38.5 ± 1.5	N/S[a]	8.2 ± 0.3	13	1T	Manual tracing
Musen	2006	82 (33)	80 (2)	32.6 ± 3.2	31.3 ± 5.1	20 ± 3.6	7.8 ± 1.3	82	1.5T	VBM (no modulation)
Northam	2009	106 (54)	75 (37)	20.5 ± 4.3	21.0 ± 3.8	12	9.2 ± 1.8	106	3T	VBM (no modulation)
Perantie	2007	108(62)	51 (26)	12.6 ± 2.7	12.3 ± 2.7	5.7 ± 2.9	8.4 ± 1.0	108	1.5T	VBM with modulation
Perantie	2011	75 (48)	25 (24)	12.5 ± 2.8	12.5 ± 2.6	5.5 ± 3.3	8.6 ± 1.4	75	1.5T	VBM with modulation
Wessels	2006	31 (12)	21 (7)	40.6 ± 6.0	36.3 ± 7.9	23 ± 12	7.6 ± 1.0	31	1.5T	VBM (no modulation)
Wessels	2007	25 (10)	9 (3)	42.2 ± 4.8	40.9 ± 8.5	26.3 ± 8.5	8.0 ± 1.1	25	3T	Automated segmentation
Van Elderen	2011	51 (30)	34(17)	44 ± 11	46 ± 14	28.8 ± 7.9	7.9 ± 1.1	15	1.5T	VBM with modulation

Age of patients and controls is presented as the mean age in years and standard deviation (SD). Mean duration of diabetes is presented in years. HbA1c: mean and SD are presented. T = Tesla; N/S = not stated.

Table 2: Key demographic, diabetes and imaging characteristics for T2DM studies

Paper (1st author)	Year	Number of patients (male)	Number of controls (male)	Age of patients (mean ± SD)	Age of controls (mean ± SD)	Diabetes duration (years)	HbA1c (%) (mean ± SD)	Number receiving insulin therapy	MRI magnet strength (Tesla)	Image processing technique
Alosco	2013	23 (12)	52 (32)	66.1 ± 6.7	69.0 ± 8.5	N/S	N/S	N/S	1.5T	Automated segmentation
Anan	2011	45 (26)	41 (N/S)	65.0 ± 6.6	N/S	11.1 ± 4.5	7.5 ± 1.0	0	1.5T	VBM (no modulation)
Anan	2010	43 (N/S)	41 (N/S)	65.0 ± 7.6	N/S	11.2 ± 4.3	7.5 ± 0.9	0	1.5T	VBM (no modulation)
Bruehl	2009	18 (10)	12 (8)	57.7 ± 8.2	62.3 ± 6.8	5.9 ± 3.8	8.1 ± 2.0	0	1.5T	Manual tracing
Brundel	2010	56 (27)	30 (13)	70.0 ± 5.2	68.1 ± 4.3	13.6 ± 6.8	7.1 ± 1.0	27	1.5T	Automated probabilistic segmentation
Chen	2011	16 (4)	16 (4)	61.2 ± 7.8	59.6 ± 6.1	13.2 ± 5.6	8.4 ± 1.7	N/S	1.5T	VBM with modulation
de Bresser	2010	55 (26)	28 (12)	65.9 ± 5.4	64.2 ± 4.3	9.5 ± 6.6	7.0 ± 1.1	17	1.5T	Automatic probabilistic segmentation
Den Heijer	2003	41 (27)	435 (233)	77.0 ± 8.0	73.0 ± 8.0	N/S	N/S	N/S	1.5T	Manual tracing
Espeland	2013	145 (0)	1221 (0)	78.1 ± 0.3	78.6 ± 0.1	N/S	N/S	N/S	1.5T	Automated segmentation
Gold	2007	23 (11)	23 (11)	59.2 ± 8.4	59.9 ± 8.6	6.0 ± 6.3	6.9 ± 0.8	0	1.5T	VBM with modulation
Hayashi	2011	61 (34)	53 (25)	74.0 ± 7.0	74.0 ± 5.0	16 ± 10	9.5 ± 2.1	47	1.5T	VBM (no modulation)
Hempel	2012	40 (22)	47 (24)	58.9 ± 8.5	60.0 ± 8.0	7.0 ± 6.3	7.9 ± 1.7	N/S	1.5T	Manual tracing
Jongen	2007	99 (49)	46 (20)	65.9 ± 5.6	64.9 ± 5.6	8.7 ± 6.1	6.8 ± 1.2	29	1.5T	Automated probabilistic segmentation
Kamiyama	2010	28 (14)	28 (14)	70.7	N/S	13.8 (1-25)	8.0 (5-14.4)	19	1.5T	VBM (no modulation)
Korf	2006	202 (202)	204 (204)	81.7 ± 5.1	81.3 ± 4.9	N/S	N/S	10	1.5T	Manual tracing
Kumar	2008	52 (13)	25 (5)	56.7 ± 9.1	53.2 ± 9.1	10.2 ± 8.5	7.5 ± 1.4	11	1.5T	Automated segmentation
Last	2007	26 (13)	25 (13)	61.6 ± 6.6	60.4 ± 8.6	12.9 ± 11.3	7.1 ± 1.0	9	1.5T	Automated segmentation
Manor	2012	97 (52)	89 (43)	64.7 ± 7.8	65.3 ± 8.2	10.8 ± 7.9	7.1 ± 1.2	N/S	1.5T	Automated segmentation
Musen	2012	10 (7)	11(7)	56.0 ± 7.0	54.0 ± 6.0	6.1 ± 0.9	7.5 ± 0.5	5	3T	Automated segmentation
Novak	2011	71 (40)	76 (33)	65.2 ± 0.7	65.2 ± 0.7	10.5 ± 1.0	7.1 ± 0.1	15	3T	Automated segmentation
Tiehuis	2008	151 (120)	892 (705)	61.5 ± 9.6	58.1 ± 10.3	8.1 ± 7.1	N/S	50	1.5T	Automated segmentation
Watari	2008	44 (14)	22 (4)	57.5 ± 9.4	52.6 ± 8.3	10.0 ± 7.9	7.4 ± 1.4	N/S	1.5T	Automated segmentation
Yau	2010	18 (N/S)	16 (N/S)	16.5 ± 1.9	17.2 ± 1.5	N/S	8.3 ± 4.8	N/S	1.5T	Automated segmentation

Age of patients and controls is presented as the mean age in years and standard deviation (SD). Mean duration of diabetes is presented in years. HbA1c: mean and SD are presented. T = Tesla; N/S = not stated.

Table 3: Volumetric meta-analysis results in T2DM

| Region studied	Number of studies	Hedge's g	95% confidence interval: lower limit	95% confidence interval: upper limit	z-value	p-value	I^2 heterogeneity quantifier
Brain parenchymal fraction	2	-0.65	-0.81	-0.48	-7.77	<.0001	0
Total brain volume	4	-0.32	-0.55	-0.094	-2.77	0.0057	36%
Frontal lobe	6	-0.22	-0.43	0.0065	-1.90	0.057	44%
Grey matter	8	-0.43	-0.60	-0.25	-4.75	<.0001	35%
Hippocampus	7	-0.88	-1.36	-0.41	3.67	0.0002	86%
Occipital lobe	3	-0.16	-0.30	-0.011	-2.11	0.035	0
Anterior cingulated	2	-0.042	-0.45	0.37	-0.20	0.84	0
Orbitofrontal cortex grey matter	2	-0.70	-1.10	-0.28	-3.29	0.001	0
Parietal lobe	3	-0.20	-0.48	0.077	-1.41	0.16	58%
Basal ganglia	3	-0.35	-0.61	0.087	-2.61	0.009	0
Temporal lobe	4	-0.13	-0.27	0.0089	-1.84	0.067	0
Superior temporal gyrus	3	-0.062	-0.43	0.30	-0.33	0.74	0

Volumetric meta-analysis is presented as Hedge's for each region analysed (standardised mean difference), 95% confidence interval, z-value and p-value, as well as the heterogeneity quantifier I^2 for each area of interest.
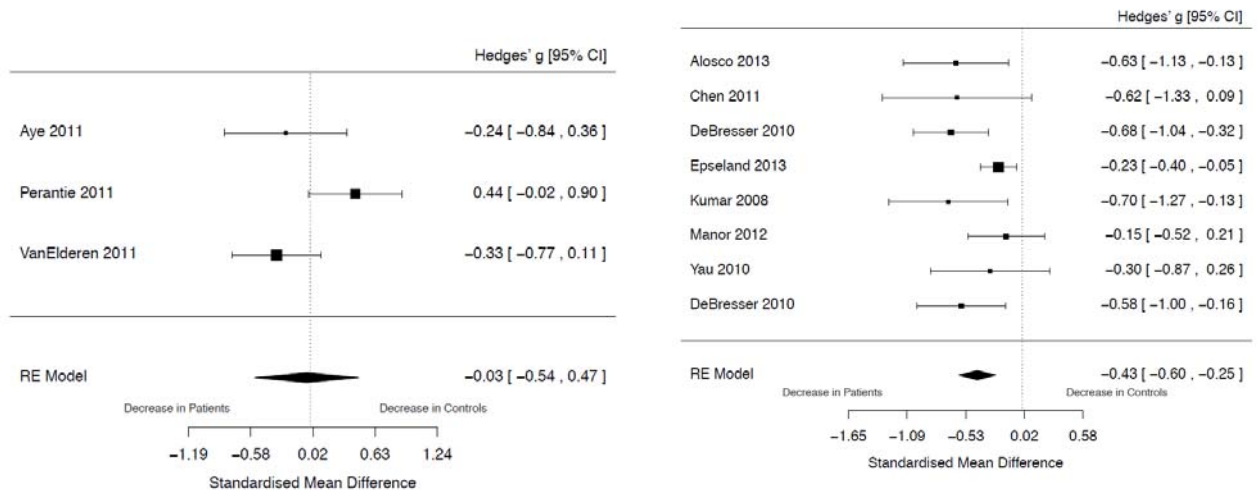
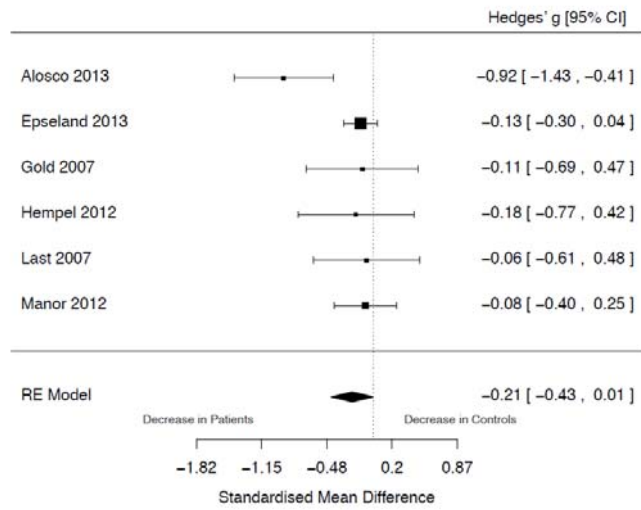# Supplementary Figures

Supplementary Figure 1
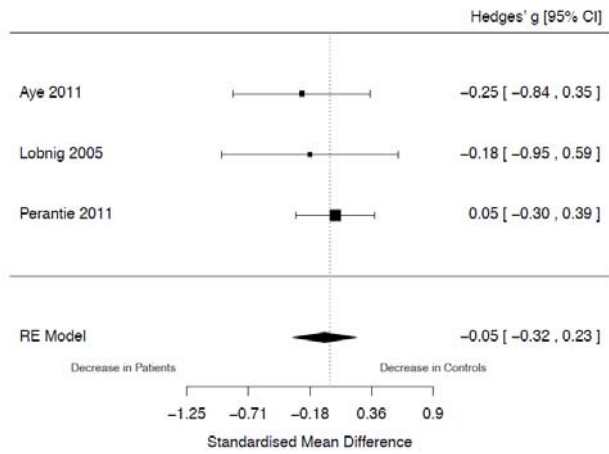
Supplementary Figure 2
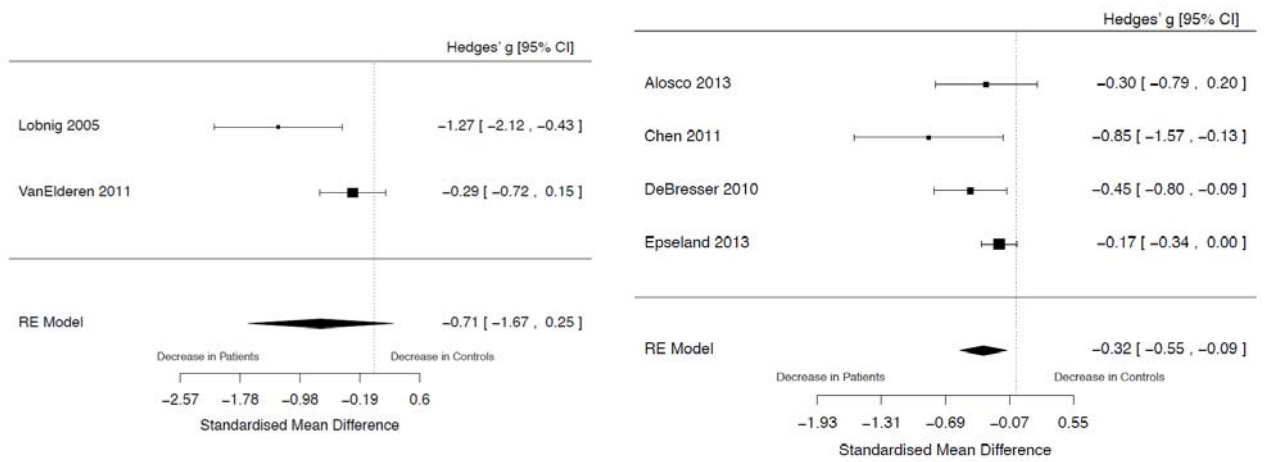
Supplementary Figure 3

Supplementary Figure 4

Supplementary Tables

Supplementary Table 1: Potential confounding variables for T1DM studies

Paper (first author)	Year	Corrected for Intra-cranial Volume	Dementia Excluded	Depression Excluded	Stroke Excluded	No. patients Hyper-lipidemia	No. controls Hyper-lipidemia	No. patients HTN	No. controls HTN	Previous severe or recurrent hypo-glycemia (% of T1DM group)
Aye	2011	No	No	No	No	N/S	N/S	N/S	N/S	29.6
Hershey	2010	Yes	Yes	Yes	Yes	N/S	N/S	N/S	N/S	61.1
Lobnig	2005	No	Yes	Yes	Yes	N/S	N/S	10	0	23.1
Musen	2006	N/S	No	Yes	No	N/S	N/S	N/S	N/S	62.2
Northam	2009	N/S	No	No	Yes	N/S	N/S	N/S	N/S	41.5
Perantie	2007	N/S	Yes	Yes	Yes	N/S	N/S	N/S	N/S	61.1
Perantie	2011	No	Yes	Yes	Yes	N/S	N/S	N/S	N/S	25.3
Wessels.	2006	N/S	Yes	Yes	Yes	N/S	N/S	0	0	0
Wessels	2007	N/S	Yes	Yes	Yes	N/S	N/S	0	0	0
Van Elderen	2011	Yes	No	No	Yes	N/S	N/S	0	0	N/S

Key: HTN = hypertension, N/S = not stated

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Supplementary Table 2: Potential confounding variables for T2DM studies

Paper (first author)	Year	Corrected for Intracranial Volume	Dementia Excluded	Depression Excluded	Stroke Excluded	No. patients Hyper-lipidemia	No. Controls Hyper-lipidemia	No. patients HTN	No. controls HTN
Alsosco	2013	Yes	Yes	No	Yes	18	31	21	34
Anan	2011	N/S	Yes	No	No	11	N/S	18	N/S
Anan	2010	N/S	Yes	No	No	10	N/S	16	N/S
Bruehl	2009	Yes	Yes	Yes	Yes	N/S	N/S	14	6
Brundel	2010	No	Yes	Yes	No	40	15	42	10
Chen	2011	No	Yes	No	Yes	N/S	N/S	6	0
de Bresser	2010	No	Yes	Yes	Yes	33	13	36	8
Den Heijer	2003	Yes	Yes	No	No	N/S	N/S	N/S	N/S
Espeland	2013	Yes	Yes	No	No	N/S	N/S	N/S	N/S
Gold	2007	Yes	Yes	Yes	Yes	N/S	N/S	14	3
Hayashi	2011	N/S	Yes	No	Yes	N/S	N/S	N/S	N/S
Hempel	2012	Yes	Yes	Yes	Yes	N/S	N/S	14	6
Jongen	2007	No	Yes	Yes	No	69	19	70	13
Kamiyama	2010	N/S	Yes	No	Yes	N/S	N/S	N/S	N/S
Korf	2006	No	No	No	No	N/S	N/S	111	84
Kumar	2008	Yes	Yes	Yes	Yes	N/S	N/S	N/S	N/S
Last	2007	Yes	No	No	Yes	10	7	8	0
Manor	2012	Yes	No	No	Yes	N/S	N/S	33	30
Musen	2012	Yes	No	No	No	N/S	N/S	5	2
Novak	2011	Yes	Yes	No	Yes	47	29	31	19
Tiehuis	2008	Yes	No	No	No	118	705	106	428
Watari	2008	No	Yes	No	Yes	N/S	N/S	14	4
Yau	2010	No	Yes	Yes	Yes	N/S	N/S	5	4

Key: HTN = hypertension, N/S = not stated

Supplementary Table 3: Volumetric meta-analysis results in T1DM

Region studied	Number of Studies	Hedge's g	95% confidence interval: lower limit	95% confidence interval: upper limit	z-value	p-value	I^2 heterogeneity quantifier
Total brain volume	2	-0.71	-1.67	0.25	-1.45	0.15	76%
Grey matter	3	-0.035	-0.54	0.47	-0.13	0.89	69%
Hippocampus	3	-0.046	-0.32	0.23	-0.32	0.75	0

Volumetric meta-analysis is presented as Hedge's for each region analysed (standardised mean difference), 95% confidence interval, z-value and p-value, as well as the heterogeneity quantifier I^2 for each area of interest.

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