

Moderate hypoglycaemia after learning does not affect memory consolidation and brain activation during recognition in non-diabetic adults

Roderick E. Warren¹
Andrew J. Sommerfield¹
Andrea Greve²
Kate V. Allen¹
Ian J. Deary³
Brian M. Frier^{1*}

¹Department of Diabetes, Royal Infirmary of Edinburgh, UK

²Department of Informatics, University of Edinburgh, UK

³Department of Psychology, University of Edinburgh, UK

*Correspondence to: Brian M. Frier, Department of Diabetes, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh EH16 4SA, United Kingdom. E-mail: brian.frier@luht.scot.nhs.uk

Abstract

Introduction Some aspects of memory performance are impaired during acute hypoglycaemia. The hippocampus is critical to formation of long-term memory, and may be particularly sensitive to hypoglycaemia. This study examined whether moderate hypoglycaemia occurring after learning would disrupt the consolidation process, and used functional magnetic resonance imaging (fMRI) to identify accompanying changes in brain activation.

Methods Sixteen non-diabetic subjects each underwent two glucose clamp studies. During euglycaemia (4.5 mmol/L), subjects tried to memorize a series of words and a series of pictures of faces. Then, either hypoglycaemia (2.5 mmol/L) was induced for one hour, or euglycaemia was maintained. During subsequent uncontrolled euglycaemia, subjects' recognition of the word and face stimuli was tested, with simultaneous fMRI to measure brain activation during recognition.

Results Face identification scores were 67.2% after euglycaemia and 66.9% after hypoglycaemia ($p = 0.895$). Word identification scores were 78.0 and 77.1% respectively ($p = 0.701$). Analysis of the fMRI identified two foci where activation was altered after hypoglycaemia compared with euglycaemia, but these were not in regions associated with memory, and were probably statistical artefacts.

Conclusions One hour of hypoglycaemia at 2.5 mmol/L induced 20–40 min after learning did not disrupt memory consolidation. fMRI did not show evidence of altered brain activation after hypoglycaemia. Consolidation may be relatively resistant to hypoglycaemia, or may have been complete before hypoglycaemia was induced. The study was powered to detect a large effect, and provides some reassurance that moderate hypoglycaemia does not cause major disruption of previously learned memories in people with insulin-treated diabetes. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords diabetes; hypoglycaemia; memory; consolidation; functional imaging

Introduction

Cognitive abilities, ranging from simple motor tasks and basic sensory processing to complex reasoning, are adversely affected by hypoglycaemia [1]. We have demonstrated previously that episodic short-, working- and long-term memory are significantly impaired by hypoglycaemia [2–4]. These

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results are in agreement with earlier reports, which included some tests of memory among broader cognitive test batteries, but much remains to be elucidated about the functioning of memory during hypoglycaemia.

Memory has been conceptualized as composed of three main subsystems: sensory memory, short-term memory, and long-term memory [5]. Sensory memory is the brief retention of an auditory or visual impression after the stimulus has been removed. Short-term memory can hold a limited number of items, with a duration measured in seconds. Long-term memory is durable, with no quantifiable capacity limits. The conversion of short- to long-term memory is known as consolidation. The neurological basis of consolidation is not well understood, but the medial temporal lobe structures appear to be critical. Evidence comes from individuals who have sustained focal damage to the hippocampus and have developed near-total inability to form new long-term memories, while retaining intact short-term memory and pre-formed long-term memories [6–9]. Cases have been reported of individuals who have developed amnesia following severe hypoglycaemia, in whom frontal and hippocampal lesions were identified on magnetic resonance imaging (MRI) scans [10,11]. A similar distribution of lesions was reported on MRI scans in four patients in a vegetative state following severe hypoglycaemia [12], and from post-mortem examinations following fatal hypoglycaemia in a human case report [13], and in an experimental rat study [14]. The frontal lobes and hippocampal region appear to be particularly sensitive to hypoglycaemia, and this may contribute to the disruptive effects of moderate hypoglycaemia on aspects of memory.

In most previous studies of memory during hypoglycaemia, both stimulus presentation and recall testing took place during the experimental condition (hypoglycaemia or euglycaemia), and so these studies could not distinguish the effects of hypoglycaemia on acquisition (learning), recall, and consolidation. We have recently demonstrated that moderate hypoglycaemia impairs both learning and recall [15]. If hypoglycaemia also impairs consolidation, then depending on the duration of the consolidation process, it could impair recall of information learned prior to the onset of hypoglycaemia.

The present study investigated whether a period of hypoglycaemia occurring immediately after exposure to new stimuli impaired subsequent recognition. Functional magnetic resonance imaging (fMRI) was used to examine brain activation during the recognition task. It was hypothesized that activation in the hippocampus and adjacent medial temporal lobe structures would be reduced following hypoglycaemia. fMRI exploits a natural difference in the magnetic properties of oxy-haemoglobin and deoxy-haemoglobin [16], such that the blood-oxygen level dependent signal is increased following neuronal activation [17,18]. Previous fMRI studies have shown that activation of the medial temporal lobe structures (including the hippocampus) is consistently associated with successful encoding and retrieval of episodic memories [19–23].

Methods

The study was approved by the local research ethics committee, and all subjects provided informed consent.

Subjects

Sixteen right-handed non-diabetic adults (9 male) for whom English was a first language were recruited. People with active medical conditions or previous history of seizure, cerebral injury, or other contra-indication to experimental hypoglycaemia were excluded. Median age was 25 years (range 20–44) and median body mass index was 22.6 kg m⁻² (range 20.1–27.7).

Study outline and glucose clamp procedure

Subjects underwent two glucose clamp studies (hypoglycaemia and euglycaemia), preceded by overnight fasting, and separated by at least two weeks. Soluble human insulin was infused intravenously at a fixed rate (60 mU/min/m² body surface area), and 20% dextrose was infused at a variable rate to achieve target blood-glucose concentrations. Samples for measurement of whole blood glucose were drawn every 3–5 min from a vein in the non-dominant hand, which was placed within a heated blanket to arterialize venous blood.

The study design is illustrated in Figure 1. During an initial euglycaemic phase, blood-glucose concentrations were stabilized at 4.5 mmol/L for 30 min, and the series of faces and words were presented for learning. In hypoglycaemia studies, the glucose infusion rate was immediately reduced to lower blood glucose quickly to a target of 2.5 mmol/L (deemed to be achieved when measurements over at least 6 min were in the range 2.3–2.7 mmol/L), maintained at this level for 60 min, and finally raised to 4.5 mmol/L, when the clamp was discontinued. In euglycaemia studies, blood glucose was maintained at 4.5 mmol/L for 100 min, including 40 min to match the time taken to achieve and reverse hypoglycaemia.

After discontinuation of the clamp, subjects were given a meal and allowed to rest for 1 h to ensure recovery of

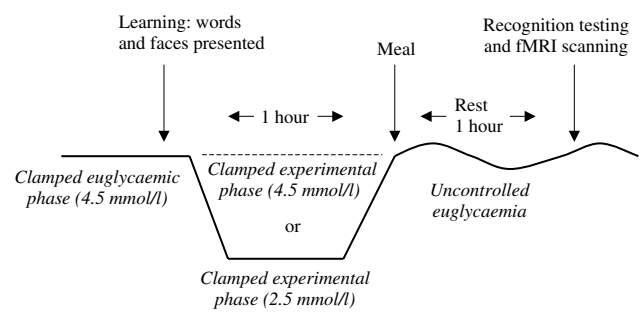


Figure 1. Sequence of experimental procedures

cognitive function. Subjects were then taken to the MRI suite for recognition testing and fMRI acquisition.

Memory tests, procedure and analysis

Face stimuli were digitized photographs of a Caucasian student population, taken without jewellery or spectacles, and scaled so that the head occupied 80% of the frame. Word lists were made up of words with frequencies between 20 and 30 in the series from Kucera & Francis [24]. Two learning batteries of 40 faces (20 male, 20 female) and 50 words were created. Tests in separate subjects prior to the commencement of this study yielded recognition rates of approximately 70% after an interval of 2 h.

A different learning battery was presented at each subject's two study sessions. Stimuli were presented on a computer screen positioned at arms length. To improve retention, subjects were asked to rate each word or face for its attractiveness, although these data (which are not relevant to the current study) were not analysed. During the next hour subjects completed tests of fluid intelligence (Raven's Advanced Progressive Matrices and the Alice Heim V test), to prevent rehearsal of learned material, and to address a separate research question; results of these have been published elsewhere [25].

Recognition was tested when subjects were in the MRI scanner. Subjects viewed stimuli on a screen directly above their faces, with focal aids if required. Stimuli were presented using E-prime Version 1.0 (Psychology Software Tools Inc, Pittsburgh, USA) and IFIS 1.09 (MRI Devices Corporation, Waukesha, USA). Following an initial practice run, subjects viewed 90 faces, of which 40 had been seen before (targets) and 50 were new (decoys). Subjects identified targets and decoys by pressing left- and right-hand buttons. Word recognition was tested with 140 words, comprising 50 targets and 90 decoys.

Performance was analysed using repeated-measures analysis of variance. Order of glycaemic condition and order of stimulus battery were counterbalanced within the experimental design, and were included as between-subjects factors. Analyses were performed using SPSS 11.0 (SPSS Inc, Chicago, USA).

Imaging acquisition and analysis

Scanning was carried out on a 1.5T GE Signa scanner fitted with EchoSpeed gradients, using the standard head coil. Acquisition periods were 540 (face paradigm) and 840 s (word paradigm); the first 10 s were discarded to ensure steady-state magnetization. Contiguous gradient echo, echoplanar images (TR 2500 ms, TE 40 ms) were collected from 30 5mm slices (interleaved acquisition) parallel to the anterior–posterior commissure plane. The matrix acquired was 64 × 64 with an in-plane resolution of 3 × 3 mm. Button responses to the memory tasks were logged simultaneously. A T1-weighted structural scan was

acquired after fMRI acquisition. Images in each series were registered to the initial image to correct for head motion. EPI-volumes were then co-registered to the T1-weighted structural volume and aligned to standard coordinates, and data was smoothed with a 6 mm Gaussian kernel to allow for variability in gyral anatomy and location of activation between subjects.

The fMRI design for the test was event-related. Data were analysed using the statistical parametric mapping package SPM99. Events were modelled using canonical haemodynamic response functions and six movement regressors. Events were classified by subject responses as 'Correct Hit', 'Correct Rejection', 'Incorrect Hit', or 'Incorrect Rejection'. For a small number of events no response was given, and these were assigned to the relevant incorrect category. First-level fixed-effects T-contrasts were made between the euglycaemia and hypoglycaemia conditions. The T threshold was set at 3.09, and cluster size threshold at 10 voxels. A fixed-effects analysis was performed, with a view to further analysis if this produced promising results.

Results

Blood glucose and timing

Comparisons for hypoglycaemic (H) and euglycaemic (E) sessions were as follows. Mean (SD) blood glucose during the initial euglycaemic phase was 4.4 (0.2) mmol/L (H) versus 4.3 (0.2) mmol/L (E), $p = 0.436$. Mean (SD) blood glucose during the experimental phase was 2.5 (0.2) mmol/L (H) versus 4.4 (0.3) mmol/L (E). In hypoglycaemia sessions, mean (SD) time to achieve stable hypoglycaemia was 30 (7) min. Mean (SD) interval between discontinuation of clamp and commencement of memory testing was 86 (10) min (H) versus 85 (15) min (E), $p = 0.803$.

Memory performance

Stimuli correctly identified were converted into a percentage, weighted for the true frequency of targets and decoys so that the chance score was 50%. Adjusted face identification scores were almost identical following euglycaemia and hypoglycaemia [67.2 (8.2) % and 66.9 (7.4) % respectively; $\eta^2 = 0.002$, $p = 0.895$], as were adjusted word identification scores [78.0 (8.0) % and 77.1 (12.2) % respectively; $\eta^2 = 0.013$, $p = 0.701$].

There was variation in the time intervals between learning and attainment of hypoglycaemia, and between learning and testing. Memory performance was re-analysed with these intervals as covariates, but all effects remained clearly non-significant. There were also no significant effects for unadjusted scores (e.g. number of correct hits). No individual memory item was very easy (correctly identified by >13 subjects) or very hard (correctly identified by <3 subjects).

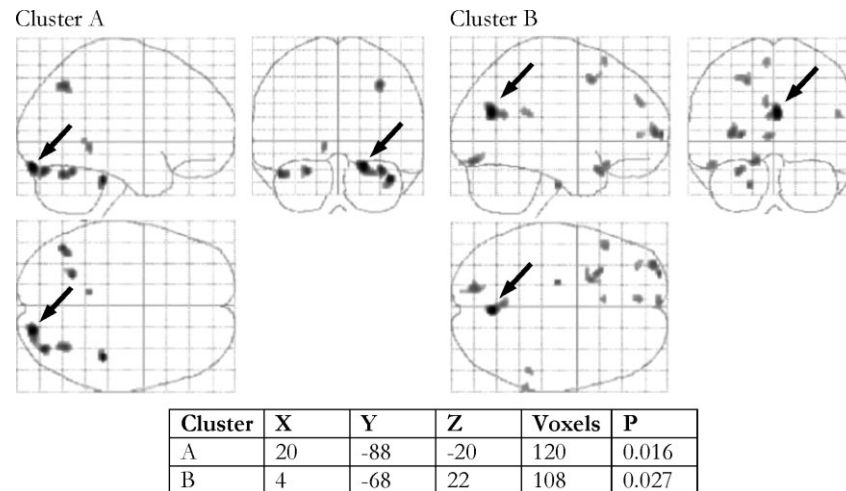


Figure 2. Brain activation maps showing clusters achieving $p < 0.05$ for hypoglycaemia versus euglycaemia. Cluster A showed significantly less activation following hypoglycaemia for faces correctly identified as targets. Cluster B showed significantly more activation following hypoglycaemia for all faces

Post hoc calculation indicated that the study had 80% power to detect a difference in adjusted face scores of 6.6 (0.8 euglycaemia SD), and in adjusted words scores of 6.9 (0.86 euglycaemia SD).

Brain activation

One brain area appeared to show glycaemic differences in recognition-associated activation (Figure 2, cluster A). This cluster is located on the border of the right occipital cortex and cerebellum, and showed reduced activation after hypoglycaemia for faces correctly identified as targets. A second area (Figure 2, cluster B) in the midline close to the calcarine sulcus showed increased activation following hypoglycaemia for all faces, irrespective of response.

Neither area is known to be associated with memory. The statistical significance is borderline using the liberal fixed-effects model, and in the absence of any results requiring further exploration, a more conservative random-effects analysis was not performed.

Discussion

No effect of hypoglycaemia on memory performance was seen in the present study. It is possible that hypoglycaemia has no effect on consolidation, but at least five alternative explanations can be proposed. In this sense, the null findings are helpful to further research.

First, the study may have been underpowered, as advance sample size estimates were limited by a lack of previous data. *Post hoc* calculations showed that the study had good power to detect a 'large' effect, according to Cohen's conventions [26]. We previously published a study of hypoglycaemia during learning and recall of verbal and visual material (this was carried out after the present study and could not inform its sample size)

[15]. The greatest effect of hypoglycaemia was seen for delayed verbal memory, with a 'medium' effect equivalent to approximately 0.6 standard deviations. A *post hoc* calculation reveals that for 80% power to detect a similar effect on the word task in the present study, a sample size of 31 would have been needed. However, although not statistically rigorous, the almost identical results following euglycaemia and hypoglycaemia do not support the possibility of an effect failing to achieve significance.

Second, the level of hypoglycaemia induced (2.5 mmol/L) may have been insufficient. Although it is known that the entire memory process from learning to recall is affected by hypoglycaemia at 2.5 mmol/L [2,3], more profound hypoglycaemia may be necessary to disrupt consolidation.

Third, hypoglycaemia may have been achieved too late (20–40 min after stimulus exposure) to affect consolidation. The duration of the consolidation process is not clearly defined. Diverse interventions have been shown to affect memories acquired minutes or hours beforehand, including drug administration [27–29] and concussion [30]. There is also substantial evidence for the improving effects of sleep, immediately or overnight, on memory consolidation [31,32]. Other studies have shown evidence of consolidation over much longer time periods. Recognition-associated fMRI brain activation progressively decreased in the hippocampus and increased in the pre-frontal region when measured 1, 2, 30 and 90 days after stimulus exposure [31], and patients with focal hippocampal lesions display a temporal gradient for amnesia over years [33–35], suggesting transfer of memory from hippocampal to other sites. In summary, consolidation appears to be a chronic and heterogeneous process. There may be an early phase (e.g. less than 20 min after learning) which is susceptible to acute metabolic derangement; if so, a different result might be expected if hypoglycaemia could be induced instantaneously, but this would not be relevant to people

with diabetes, in whom hypoglycaemia may develop over hours [36].

Fourth, it is possible that the brain may work harder, or differently by recruitment of other regions, to achieve the same result during hypoglycaemia. However, the fMRI data revealed apparent differences in activation for hypoglycaemia and euglycaemia in only two brain areas, neither of which are associated with memory, and a liberal fixed-effects analysis yielded only borderline statistical significance. We conclude that the functional imaging showed no evidence of altered brain functioning following hypoglycaemia.

Fifth, the present study measured recognition rather than recall, because of logistical difficulties in obtaining anything other than binary answers during MRI scanning. Recognition may require less robust encoding, and hence suffer less disruption from hypoglycaemia. However, recognition tasks have been used effectively in fMRI memory studies [19], and a recognition task was adequate to show changes in both memory performance and brain activation following an intervention to affect consolidation [31]. The memory tasks in the present study had not been used previously, but the results suggest that they were valid: scores fell appropriately between floor (50%) and ceiling (100%) limits, with no very easy or difficult items.

Non-diabetic subjects were studied because of the difficulties of maintaining infusions in an MRI room, required for diabetic subjects to prevent unacceptable variations in blood glucose. However, most previous studies that have compared the cognitive effects of hypoglycaemia in diabetic and non-diabetic subjects have reported either similar results, or relative resistance to cognitive dysfunction in diabetic subjects [37]. It seems unlikely that a positive result would be obtained in diabetic subjects but a null result in non-diabetic subjects.

Jauch-Chara *et al.* recently reported the effects of hypoglycaemia on overnight memory consolidation [38]. Word pair recall was tested before and after sleep, on hypoglycaemia nights (nadir blood glucose 2.2 mmol/L induced 60 min after sleep onset) and control nights. Performance improved after control nights, consistent with the known effects of sleep on consolidation, but no improvement occurred over hypoglycaemia nights. The results suggest that hypoglycaemia did disrupt consolidation, and it is instructive to compare that study with the present study. First, Jauch-Chara *et al.* did not report a significant effect of hypoglycaemia in subsets of 16 diabetic and 16 non-diabetic subjects, but in all 32 subjects combined. This is consistent with the sample size estimate of 31 mentioned above, and tends to reinforce the lack of power of the present study. Second, consolidation while asleep may be a different phenomenon from consolidation awake while. Sleep appears to be a time of active re-processing of memory, and therefore, perhaps a time of increased susceptibility to memory interventions [39].

Other researchers have managed to study brain activation during hypoglycaemia. Using very long tubing

to infusion pumps outside the MRI field, Rosenthal *et al.* examined the effects of hypoglycaemia (2.5 mmol/L) on fMRI brain activation during finger tapping and reaction time tasks in non-diabetic subjects [40]. By comparison with euglycaemia, during hypoglycaemia there was increased activation in the parietal association area, and decreased activation in the visual cortex, cerebellum, hippocampus, and pre-motor cortex. The hippocampus was the only one of these areas that was not activated by the cognitive tasks. Teves *et al.* used positron emitting tomography (PET) to measure cerebral blood flow (CBF) during passive hypoglycaemia (3.0 mmol/L) in non-diabetic subjects [41]. Global CBF fell by 6–8% during hypoglycaemia, but with a relative increase in CBF in the thalamus, medial pre-frontal cortex and right orbital pre-frontal cortex, and a 26% relative decrease in CBF in the hippocampus. Anderson *et al.* reported that occipital activation during visual stimulation was reduced during hypoglycaemia (2.8 mmol/L) in non-diabetic subjects [42]. Wessels *et al.* studied activation during a working memory test, and found increased activation in the anterior cingulate and orbital frontal gyrus during hypoglycaemia (~2.3 mmol/L) in subjects with advanced diabetic retinopathy compared with subjects with no retinopathy [43]. This was interpreted as an altered brain response compensating for cerebral microvascular damage, for which retinopathy is a proxy. It is impossible to amalgamate these studies to obtain a coherent account of changes in activation throughout the brain, but the hippocampus stood out as having reduced fMRI activation or CBF during hypoglycaemia in the studies by Rosenthal *et al.* and Teves *et al.*, [40,41]. Given the sensitivity of the hippocampus to hypoglycaemic damage [12–14], it seems plausible that hippocampal dysfunction during moderate hypoglycaemia contributes to memory impairment.

In summary, 1 h of hypoglycaemia at 2.5 mmol/L after stimulus exposure did not affect subsequent recognition performance, and did not alter brain activation patterns during recognition. A large effect of moderate hypoglycaemia on memory consolidation can be excluded, and thus, the study provides some limited reassurance relevant to diabetic daily life. In retrospect, the study was underpowered to detect an effect of hypoglycaemia on memory comparable to effects seen in other studies, and future studies should probably aim to recruit 30 or more subjects. It is possible that more profound hypoglycaemia would yield a different result. It would be of interest in future to compare regional brain activation responses to memory and non-memory tasks during hypoglycaemia, and to vary the delay before induction of hypoglycaemia, and the level of hypoglycaemia achieved.

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Conflict of interest

None declared.

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