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Glucose modulates event-related potential components

of recollection and familiarity in healthy adolescents

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RUNNING HEAD: Glucose ingestion, ERPs and recognition memory

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Abstract

Behavioural evidence supports the notion that oral glucose ingestion enhances recognition memory judgements based on recollection, but not familiarity. The present study sought to clarify and extend upon these behavioural findings by investigating the influence of glucose administration on event-related potential (ERP) components that are thought to be differentially mediated by recollection and familiarity processes in healthy adolescents. In a within subjects design, participants performed a recognition memory task, during which time EEG was recorded, subsequent to ingestion of either a) glucose, or b) placebo in a counterbalanced order. Response times during the recognition memory task were observed to be faster for the glucose condition, relative to a placebo control. Further, glucose ingestion was associated with an enhanced left parietal old/new ERP effect (a marker of recollection) and an enhanced mid-frontal old/new ERP effect (known to be mediated by familiarity). These findings a) support the results of previous research that the 'glucose memory facilitation effect' can be extended to healthy adolescents, but b) suggest that glucose enhances both the recollection and familiarity components of recognition memory. The observed ERP profile has important implications for the proposal that glucose specifically targets the hippocampus in modulating cognitive performance.

The facilitatory effect of acute glucose administration on memory is now well established (for a review see Messier 2004). Oral glucose ingestion has been observed to improve cognitive performance in individuals with memory deficits (Manning *et al.* 1998; Pettersen and Skelton 2000; Watson and Craft 2004; Stone and Seidman 2008), the elderly (Craft *et al.* 1994; Riby *et al.* 2004; Riby *et al.* in press) and healthy younger adults (Benton *et al.* 1994; Foster *et al.* 1998; Sünram-Lea *et al.* 2001; Meikle *et al.* 2005). Glucose has also been associated with memory improvements in children (Horne *et al.* 2006; Benton and Stevens 2008) and adolescents (Smith and Foster 2008a; Smith and Foster 2008b). However, the specific neurocognitive mechanisms underlying the 'glucose memory facilitation effect' remain uncertain.

It is now widely accepted that recognition memory is underpinned by two neurocognitive processes, namely 'recollection' and 'familiarity' (for reviews see Yonelinas 2002; Eichenbaum *et al.* 2007; Mandler 2008). In this context, recollection can be defined as memory for an event with retrieval of accompanying spatiotemporal contextual details, whereas familiarity does not involve this degree of episodic richness (Tulving 1985; Aggleton and Brown 2006). It has been proposed that recollection is mediated by the hippocampus; by contrast, familiarity is thought to be subserved by the perirhinal cortex (Brown and Aggleton 2001; Aggleton and Brown 2006; Eichenbaum *et al.* 2007; but see Squire *et al.* 2007 for a conflicting view). The basis of this neuroanatomical distinction is largely predicated upon a series of hippocampal amnesic cases in which familiarity processes are relatively spared in the context of recollection deficits (e.g. Holdstock *et al.* 2002; Aggleton *et al.* 2005).

A meta-analytic review of the glucose memory facilitation effect has supported the view that verbal episodic memory is the cognitive domain that is most amenable to improvement subsequent to glucose ingestion (Riby 2004). On this basis, it has been

suggested that the hippocampus may be centrally involved in mediating the glucose memory facilitation effect (Winocur 1995; Riby 2004; Riby and Riby 2006), given that this brain structure is intimately involved in the mediation of episodic memory (Squire 1992; Shastri 2002). This 'hippocampus hypothesis' is supported by a recent functional magnetic resonance imaging (fMRI) study in which significantly increased brain activation was detected in the parahippocampus subsequent to glucose ingestion during a verbal memory encoding task in patients with schizophrenia (Stone *et al.* 2005). By contrast, other studies have found that glucose also improves performance on tasks subserved by other brain regions (e.g. Benton *et al.* 1994; Donohoe and Benton 1999; Martin and Benton 1999; Kennedy and Scholey 2000; Scholey *et al.* 2001; Scholey *et al.* 2009). Studies such as this question the robustness of the 'hippocampus hypothesis'.

Given that i) recollection is thought to be selectively mediated by the hippocampus, and that ii) there is evidence to suggest that the glucose memory facilitation effect is subserved by the hippocampus, glucose may be expected to preferentially enhance recognition memory based on recollection relative to familiarity judgements. A study by Sünram-Lea and colleagues (2008) recently addressed this question. In this study, healthy young adults were presented with a list of words subsequent to ingestion of 25 g glucose or a placebo. At a later test phase, participants were presented with a list of both studied and unstudied items, and were required to respond as to whether they had previously encountered each stimulus during the study phase. Recollection and familiarity were assessed behaviourally, in that participants respond as to whether they "remembered", "knew" or "guessed" that they had encountered a stimulus during the study phase upon responding that they had studied the item. This procedure (Gardiner and Java 1990; Gardiner and Richardson-Klavehn 2000) is based on the premise that subjective remembering reflects recollection, while knowing that a stimulus has been encountered previously without accompanying

contextual information is analogous to familiarity (Tulving 1985). Subsequent to glucose ingestion, participants demonstrated a significantly higher proportion of 'remember' responses relative to placebo ingestion (Sünram-Lea *et al.* 2008). On the basis of this observation, it was concluded that glucose selectively enhances recognition memory based on recollection, but not familiarity judgements. However, some researchers have questioned the reliability of the remember-know procedure, in that many participants may lack adequate subjective awareness to judge whether they 'remembered' or 'knew' that they had encountered a stimulus previously (Yonelinas 2002).

Event-related potentials (ERPs) provide an alternative methodology for assessing cognitive performance in situations where overt behavioural responses cannot be reliably obtained. ERPs have been employed by previous studies in which glucose influences on cognitive performance has been investigated (for a review see de Bruin and Gilsenan in press). Specifically, Geisler and Polich (1994) failed to observe glucose modulation of ERPs during a visual oddball task, in which participants were required to respond only to infrequently and irregularly presented 'target' stimuli within an array of 'standard' stimuli. However, it may well be that the task employed was not sufficiently difficult to be sensitive to the effects of glucose. In a subsequent study, glucose ingestion also failed to elicit ERP differences during a visual memory task relative to placebo in a sample of elderly individuals (Knott *et al.* 2001). On the other hand, it has been recently reported that during performance of a visual three-stimulus oddball task, glucose ingestion is associated with a shorter ERP latency for a component known to index memory storage operations and thought to be dependent on hippocampal function (P3b) in healthy young adults (Riby *et al.* 2008). Further, the ingestion of a beverage comprising a combination of glucose and caffeine has been associated with enhanced ERP components of attention and decision making during performance of a sustained visual selective attention task (Rao *et al.* 2005).

In recent years, researchers have also begun to employ ERPs as a useful tool to dissociate recollection from familiarity (Mecklinger 2006). In an old/new recognition memory paradigm, it is now well known that ERP waveforms for correct responses to old items are more positive going relative to correct rejections for new items over left parietal scalp sites during the 400-800 ms post-stimulus latency range. This ERP component is known as the 'left parietal old/new effect' (LP), and is associated with recollection (for reviews see Allan *et al.* 1998; Rugg and Curran 2007). The LP component has been linked to recollection primarily on the basis of observations that this component is modulated by subjective 'remembering' or memory for the context in which stimuli were encoded, which are established behavioural indices of recollection (Rugg and Curran 2007). Oral glucose ingestion has been observed to modulate the LP ERP component (Brown and Riby 2007). A similar ERP component is typically observed over the mid-frontal region, for which the mean ERP amplitude is typically more positive for old relative to new stimuli during the 300-500 ms post-stimulus latency range. This component has become known as the 'FN400' (Curran 1999), and is believed to reflect familiarity (for reviews see Mecklinger 2006; Rugg and Curran 2007). Initial evidence for the FN400 component as an ERP marker of familiarity was derived from 'depth of processing' studies, as behavioural findings have suggested that 'shallow' processing relies upon familiarity based recognition memory. It has been observed that the FN400 component is elicited only when studied items in a recognition memory task are 'shallowly', but not 'deeply' processed (Rugg *et al.* 1998). The FN400 component also peaks earlier than the LP component, a finding which is in line with behavioural evidence that 'familiarity' is a faster process than recollection (Curran 2000). Further, an additional 'plurality recognition' paradigm has also been derived from the traditional old/new paradigm (Hintzman and Curran 1994) in which familiarity and recollection can be dissociated using ERPs (Curran 2000). During the recognition test phase of this task, participants are presented

with items which are old (studied), new (not studied previously) or similar (opposite in plurality to studied items). ERP differences between old [correct] and similar [incorrect] trials are proposed to reflect recollection over the same scalp sites and latency range as the traditional left parietal old/new effect. Similarly, differences between similar [incorrect] and new [correct] trials are posited to be an ERP correlate of familiarity over the same scalp sites and latency range as the traditional FN400 (Curran 2000).

The aim of the present study was to investigate the influence of glucose ingestion on ERP correlates of recollection and familiarity in healthy adolescents using a recognition plurality paradigm (Hintzman and Curran 1994; Curran 2000). It was hypothesised that the ERP difference between old [correct] and new [correct] items would be greater over the left parietal scalp sites during the 400-800 ms latency range subsequent to ingestion of glucose, relative to a sweetness and appearance matched placebo. Given that this LP ERP component is known to reflect recollection, this hypothesis is consistent with the recent behavioural findings of Sünram-Lea and colleagues (2008), in which glucose was observed to enhance recognition memory based on recollection but not familiarity based judgements. Therefore, in the present study, an ERP difference was not expected between the two treatment conditions for the FN400 component. Further supplementary analyses also investigated the influence of glucose versus placebo administration on ERP differences between a) old [correct] and similar [incorrect], and b) similar [incorrect] and new [correct] waveforms.

Method

Participants

A total of 18 healthy adolescents participated in the present study (9 males, 9 females), ranging in age between 13 and 18 years (M_{age} = 14.4, SD_{age} = 1.5). Three participants were left handed. Participants were recruited from a database of individuals who had previously expressed an interested in participating in research studies in the Brain, Performance and Nutrition Research Centre at Northumbria University, UK. One participant was not able to consume the entire glucose drink and was therefore excluded from all analyses reported here. Participants were reimbursed with shopping centre vouchers to the value of £20 for participating in the present study. Ethical approval was obtained from the Ethics Committee of the School of Psychology and Sports Sciences at Northumbria University.

Treatment and Design

A within subjects design was employed. For the behavioural analyses, there were two within subjects factors. The treatment factor had two levels (glucose, placebo) and the type factor had three levels (old, similar, new). For the ERP analyses, there were also two within subjects factors. The treatment factor had two levels (glucose, placebo) and the site factor had three levels (left, midline, right).

The glucose treatment comprised 25 g glucose (dextrose) powder (myprotein.co.uk, Cheadle, Cheshire, UK) dissolved in 300 ml water. The placebo treatment comprised five Boots aspartame tablets dissolved in 300 ml water. This quantity of aspartame is matched for sweetness with 25 g glucose powder when dissolved in 300 ml water (Sünram-Lea *et al.* 2008). Participants attended two test sessions. They were administered one treatment in the first session and the complementary treatment in the second session, in a counterbalanced order.

Materials

Recognition Memory Task. The recognition memory task employed in the present study was based upon the recognition plurality procedure of Curran (Hintzman and Curran 1994; Curran 2000). Stimuli were 480 common concrete nouns with a length of 4-6 letters and a written frequency of 0-99 occurrences per million that could be pluralised by adding 's'. Items were divided into eight lists that were approximately balanced with regard to length, written frequency and concreteness (Kučera and Francis 1967). An additional 24 items were used for the practice block. The experiment was generated using E-Prime Software (Psychology Software Tools). Stimuli were presented in black, bold and capitalised 18 point courier new font on a white background at the vertical and horizontal centre of the screen.

Two versions of the task were created. Participants were administered one of these tasks in the first testing session, and the corresponding task in the second testing session, in a counterbalanced order. Each task comprised four study-test blocks. All study phases comprised 40 trials. Each study trial began with a central fixation cross for 300 ms, which was replaced by the stimulus for 750 ms. A two-minute retention interval followed each study phase during which the participants were instructed to sit quietly. The test phases comprised 60 trials. Each test trial began with a central fixation cross for 1,000 ms, which was replaced by the stimulus for up to 2,500 ms. Within each test phase, 20 items were 'old' (i.e. studied during the preceding study phase), 20 items were 'new' (i.e. not studied previously) and 20 items were 'similar' (i.e. opposite in plurality to items studied during the preceding study phase). Participants were required to depress a response key marked 'yes' if they remembered seeing the item during the study phase, or to depress a response key marked 'no' if they did not remember seeing the item previously or if the item was opposite in plurality to a studied word. Whether the 'yes' response was made with the left or right hand

was counterbalanced between participants. Responses were only possible during the 2,500 ms that the test item appeared on the screen. The test item disappeared from the screen once a response was detected and was replaced with the fixation cross for the next trial. The order of presentation of each item within blocks was randomised and the order in which each block was presented within the task was also randomised for each participant. The assignment of items to each condition (i.e. old, new or similar) was approximately counterbalanced between participants. Half of the stimuli for the 'old' and 'similar' conditions within each test block were studied in their singular form, and the other half were studied in their plural form. Likewise, half of the 'new' items appeared in their singular form and the other half in their plural form during the test phase.

Blood Glucose Equipment. Blood glucose concentration was measured using a Reflotron® automatic reflectance photometer and Reflotron® glucose reagent strips (Bio-Stat Healthcare Group, Stockport, Cheshire, UK). The fingertip was lanced using Accu-Chek Safe-T-Pro lancets (Roche Diagnostics Ltd., Burgess Hill, West Sussex, UK). 30 µL capillary blood was drawn for each test using Reflotron® capillary tubes. This blood was applied to the reagent strip for blood glucose quantification by the reflectance photometer.

Procedure

Participants attended two testing sessions. They were instructed not to consume any food or drink, other than water, two hours prior to each session. Written informed consent was obtained prior to the commencement of the first test session from participants and their parents. At this time, participants and their parents were informed that the purpose of the study was to investigate the effect of glucose ingestion on memory performance. Participants were then prepared for the EEG recording and the BioSemi headcap was fitted. Baseline blood glucose concentrations were subsequently measured, before participants completed a practice block of the recognition memory task. Participants then consumed one of the two

treatments. Participants were blind as to the contents of the drinks, told only that they comprised of a "sweet tasting liquid". Participants were allowed 10 minutes to consume their designated treatment. Ten minutes following the completion of treatment consumption, blood glucose concentrations were measured. Participants then completed the recognition memory task while EEG was recorded. They were instructed to remain as still and relaxed as possible and to maintain fixation on the centre of the screen throughout the recognition memory task, in order to reduce movement related EEG artefact. A final measure of blood glucose concentration was obtained 43 minutes post-treatment (i.e. the earliest time-point at which blood glucose concentration was feasibly able to be measured subsequent to completion of the recognition memory task). For details of the precise timings of each of the events within the study protocol, see Table 1.

A second testing session was conducted between seven and eight days after the first testing session ($M = 7.06$ days, $SD = 0.24$). The second testing session was identical to the first testing session, except that participants were administered the complementary treatment (glucose or aspartame) and version of the recognition memory task to that administered in the first testing session.

INSERT TABLE 1 ABOUT HERE

EEG Recording and Data Reduction

EEG was recorded with a 32 channel electrode cap (BioSemi Active Two), fitted with silver/ silver chloride (Ag/AgCl) active electrodes based on an extended 10-20 system (Jasper 1958; American Encephalographic Society 1994). The montage included four midline sites (Fz, Cz, Pz, Oz), 14 sites over the left hemisphere (Fp1, AF3, F3, F7, FC1, FC5, C3, T7, CP1, CP5, P3, P7, PO3, O1) and 14 sites over the right hemisphere (Fp2, AF4, F4, F8, FC2,

FC6, C4, T8, CP2, CP6, P4, P8, PO4, O2). The EEG signal was referenced to linked electrodes placed on the mastoids, band pass filtered at 0.46-30Hz and digitised at a rate of 2048 per second. Vertical electro-oculogram (VEOG) was recorded via the placement of electrodes 1.5 cm above and 1.5 cm below the left eye.

EEG epochs recorded from 200 ms pre-stimulus onset to 800 ms post-stimulus onset were extracted for averaging. EEG data was not able to be recorded for two participants due to an equipment malfunction. Automatic ocular artefact correction, artefact rejection (for trials where ERPs extended beyond the range of -100 µV to 100 µV for any channel) and ERP averaging were conducted offline using Edit 4.3 software (Neuroscan). Trials were manually scanned to verify that the automatic ocular artefact correction and artefact rejection procedure had worked effectively. ERP averages were only used for analysis if they comprised a minimum of 16 artefact-free trials. In the case that specific channels were consistently noisy throughout the testing session, these channels were averaged to the nearest channel. The mean number of excluded channels was 0.35 (SD = 0.94, range = 0-4).

EEG data was discarded from two participants due to insufficient artefact-free trials across each of the critical averages for one test session. A further participant had insufficient artefact-free trials in the similar [correct] condition, while for one additional participant there were insufficient artefact-free trials in the similar [incorrect] condition. Therefore, the total number of participants included in each of the critical averages was 13 for the old [correct] and new [correct] averages and 12 for the similar [correct] and similar [incorrect] averages.

Results

Blood Glucose Concentration

A significant treatment x time interaction effect was observed, $F(2, 15) = 31.88$, $p <$ .001, with a large effect size (partial $\eta^2 = .81$). Post-hoc Bonferroni pairwise t-tests revealed that, as anticipated, blood glucose concentrations were significantly higher for the glucose condition, relative to the placebo condition, 10 minutes, $t(16) = 3.71$, $p < .01$, and 43 minutes, $t(16) = 12.29$, $p < .001$, post-treatment delivery. Blood glucose concentrations between the glucose and placebo conditions did not differ at baseline, $t(16) = -0.55$, *n.s* (see Figure 1).

INSERT FIGURE 1 ABOUT HERE

Behavioural Results

Response Accuracy. The treatment x type interaction and main effect of treatment failed to reach significance for response accuracy. However, a significant main effect of type was observed, $F(2, 15) = 38.67$, $p < .001$, with a large effect size (partial $\eta^2 = .84$). Post-hoc Bonferroni pairwise comparisons revealed that correct rejection of new items, collapsed across both treatment conditions, was significantly greater than for old item hits, $p < .05$, and similar item correct rejections, $p < .001$.

Response Time. The treatment x type interaction failed to reach significance for response time. However, a main effect of treatment was observed, $F(1, 16) = 4.37$, $p = .05$, with a small to moderate effect size (partial $\eta^2 = .21$), in that the mean response time was faster after glucose relative to placebo. Further, a main effect of type was observed, $F(2, 15) = 5.81$, $p < .05$, with a moderate effect size (partial $\eta^2 = .44$). Post-hoc Bonferroni pairwise comparisons revealed that response time for new items, collapsed across both treatment

conditions, was significantly faster than for similar items, $p < .05$. No further post-hoc comparisons were significant.

ERP Results

Two primary ERP analyses were conducted. The first (FN400) focused on the mean amplitude for old [correct] and new [correct] trials during the 300-500 ms latency range over frontal sites F3, Fz and F4 (see Figure 2). The second component of interest (LP) focused on the mean amplitude for old [correct] and new [correct] trials during the 400-800 ms latency range over parietal sites P3, Pz and P4 (see Figure 3). Old [correct] – new [correct] ERP difference waveforms were calculated for each treatment condition and for both the FN400 and LP components. Subsequent supplementary recognition plurality effect analyses focused on similar [incorrect] – new [correct] difference waveforms during the 300-500 ms latency range over frontal sites F3, Fz and F4 (familiarity effect) and old [correct] – similar [incorrect] difference waveforms during the 400-800 ms latency range over parietal sites P3, Pz and P4 (recollection effect).

INSERT FIGURE 2 AND FIGURE 3 ABOUT HERE

Mid-frontal old/ new effect. The treatment x site interaction and main effect of site failed to reach significance for the frontal old/ new effect. However, a significant main effect of treatment was observed, $F(1, 12) = 9.80$, $p < .01$, with a moderate effect size (partial $\eta^2 = .45$): the mean amplitude difference between old stimuli hits and new stimuli correct rejections across the 300-500 ms latency range was greater for the glucose relative to the placebo condition (see Figure 4).

Left parietal old/ new effect. The treatment x site interaction failed to reach significance for the parietal old/ new effect. However, a main effect of treatment was

observed, $F(1, 12) = 4.92$, $p < .05$, with a moderate effect size (partial $\eta^2 = .29$): the mean amplitude difference between old stimuli hits and new stimuli correct rejections across the 400-800 ms latency range was greater for the glucose relative to the placebo condition (see Figure 4). Further, a main effect of site was observed, $F(2, 11) = 6.30$, $p < .05$, with a large effect size (partial $\eta^2 = .53$). Post-hoc Bonferroni pairwise comparisons revealed that ERP mean amplitude differences between old stimuli hits and new stimuli correct rejections across the 400-800 ms latency range, collapsed across both treatment conditions, were significantly greater at P3 relative to P4, $p < .05$, and at Pz relative to P4, $p < .05$.

INSERT FIGURE 4 ABOUT HERE

Recognition plurality effect. All effects were nonsignificant over the frontal sites across the 300-500 ms latency range. Likewise, all effects were also nonsignificant over the parietal sites across the 400-800 ms latency range.

Discussion

The present study investigated the influence of acute glucose administration on ERP components known to index recollection and familiarity in healthy adolescents. Subsequent to ingestion of 25 g glucose in solution or a sweetness and appearance matched placebo, electroencephalogram (EEG) was recorded during the time period when participants completed a recognition memory task. As anticipated, blood glucose concentration was significantly elevated subsequent to glucose ingestion for the glucose condition, relative to the placebo condition at time-points both before and after administration of the recognition memory task. This infers that, on average, blood glucose concentration was elevated in the glucose condition relative to the placebo condition during the recognition memory task.

It was hypothesised that glucose administration would be associated with an ERP signature consistent with enhanced recollection, relative to the placebo condition. However, no differences were expected between the two treatment conditions for ERP components reflecting familiarity. By contrast, analysis of the ERP results indicated that glucose administration enhanced both recollection and familiarity. This finding contrasts with previous behavioural evidence that glucose facilitates recognition memory based on recollection but not familiarity judgements (Sünram-Lea *et al.* 2008). However, the ERP methodology employed here represents a more reliable technique for assessing recollection and familiarity compared with the remember-know procedure employed in this previous study (Sünram-Lea *et al.* 2008). Further, faster response times were detected subsequent to glucose ingestion relative to placebo during the recognition memory task.

Specifically, ingestion of glucose was associated with a greater ERP difference between old [correct] and new [correct] trials relative to placebo, over the parietal cortex during the 400-800 ms post-stimulus onset latency range. Further, a greater ERP difference between old [correct] and new [correct] trials was detected subsequent to glucose ingestion,

relative to placebo, over the frontal region bilaterally during the 300-500 ms latency range. Taken together these findings suggest that glucose ingestion is associated with greater recollection and greater familiarity relative to ingestion of the placebo treatment. In accordance with previous work (Rugg and Curran 2007), the parietal old/new effect was maximal over the left parietal relative to the midline parietal and right parietal scalp sites. This observation confirms that the LP component detected in the present study is a true reflection of the parietal old/ new effect that is a known ERP correlate of recollection. However, there was no main effect of site for the frontal old/new effect, in accordance with previous research suggesting that this familiarity component is observable bilaterally (e.g. Rhodes and Donaldson 2007).

Given that such robust findings were observed for the frontal and parietal old/new treatment effects in the present study, it is somewhat surprising that recognition plurality ERP treatment effects were not observed in the supplementary analysis reported here. However, the recognition plurality ERP effects have been afforded relatively little attention in the literature relative to the frontal and parietal old/new effects. These recognition plurality ERP effects are therefore less well understood. Further, the processes reflected by the FN400 ERP effect have also been questioned, given the conceptual basis for this effect: specifically, that this ERP component reflects familiarity because it is not elicited by methodological procedures that are designed to evoke processes of recollection (Paller *et al.* 2007). However, while there has been some suggestion that the FN400 component is characterised by conceptual priming rather than familiarity (Paller *et al.* 2007; Stenberg *et al.* in press), the results of a recent study which incorporated a name recognition task suggest, conversely, that the FN400 component is modulated by familiarity but not conceptual priming (Stenberg *et al.* in press).

Given the previous behavioural observation that glucose ingestion modulates recollection but not familiarity (Sünram-Lea *et al.* 2008), it is somewhat surprising that a familiarity treatment effect was additionally observed for the adolescent participants in the present study. The inconsistency between the findings of this previous study and the present study may well be related to the relative unreliability of the remember-know paradigm (Yonelinas 2002) relative to the ERP methodology employed in the present study. It is also important to note that the FN400 and LP ERP components are not directly comparable to an individual judging whether recognised stimuli were 'remembered' or 'known'. However, a further key difference between the present study and the work of Sünram-Lea and colleagues (2008) is that the present study employed a sample of healthy adolescents (age range 13-18 years), whereas healthy young adults (age range 18-25 years) served as the participant group in the Sünram-Lea et al. (2008) study. Therefore, it is possible that the age difference between these two study samples could explain the discrepancy between the two studies pertaining to glucose enhancement of familiarity based recognition memory.

This discrepancy with regard to glucose facilitation of familiarity between the present study and the study of Sünram-Lea and colleagues (Sünram-Lea *et al.* 2008) is especially interesting in context of previously reported ERP findings that children do not exhibit frontal old/new effects (Czernochowski *et al.* 2005). It is worthy of note that in the present study, the FN400 ERP difference between old [correct] and new [correct] trials (i.e. the ERP signature of familiarity) was small for the placebo condition, and was significantly smaller for the placebo condition relative to the glucose condition. Therefore, there is little evidence on the basis of the present study findings for familiarity based recognition memory under control conditions, whereas glucose ingestion was associated with increased familiarity in our adolescent sample. This observation is potentially related to the notion that glucose can only be reliably observed to facilitate memory in individuals who are not able to perform at their

'cognitive peak' (Foster *et al.* 1998), for example, the elderly (Craft *et al.* 1994; Riby *et al.* 2004; Riby *et al.* in press), individuals with memory deficits (Manning *et al.* 1998; Watson and Craft 2004; Stone and Seidman 2008) or in healthy younger individuals under conditions of increased task demands (Kennedy and Scholey 2000; Scholey *et al.* 2001; Sünram-Lea *et al.* 2002). Given that familiarity has been suggested to develop relatively late in childhood (Czernochowski *et al.* 2005), it is perhaps somewhat unsurprising that the mid-frontal ERP effect was small in the placebo condition. Future research in this area should investigate whether the current finding that glucose modulates ERP components of recollection and familiarity can be generalised across different age groups.

A key motivation of the present study was to further elucidate the neurocognitive mechanisms that subserve the glucose memory facilitation effect. On the basis of previous evidence in humans (Riby 2004) and animals (Winocur 1995) that episodic memory is the cognitive domain most reliably observed to be improved subsequent to glucose ingestion, the 'hippocampus hypothesis' suggests that glucose selectively targets the hippocampus in modulating cognitive performance (Riby and Riby 2006). The notion that the hippocampus is directly involved in mediating the glucose memory facilitation effect is supported by observations that the hippocampus is densely populated with insulin receptors relative to many other brain regions (Lathe 2001). Further, glucose has been associated with increased hippocampal acetylcholine synthesis (Messier and Gagnon 1996). However, the hippocampus hypothesis does not account well for previous study findings in which non-memory tasks are improved by glucose (e.g. Donohoe and Benton 1999; Scholey *et al.* 2009). Given that recollection, but not familiarity, is believed to be supported by the hippocampus (Brown and Aggleton 2001; Aggleton and Brown 2006), the ERP results reported here also offer little support for the hippocampus hypothesis, at least in its selectively specific form. Instead, the

present study findings suggest that glucose targets more global brain regions in enhancing cognitive functioning.

Of further interest in the present study is the observation that glucose ingestion was associated with faster response times on the recognition memory task relative to the placebo condition. This finding appears to be in concordance with previous work in the literature in which increased blood glucose concentration has been associated with enhanced response times (Benton *et al.* 1994; Owens and Benton 1994). The current study finding that glucose ingestion improves response times during a recognition memory task extends previous work from our laboratory which suggests that the glucose memory facilitation effect can be generalised to healthy adolescents (Smith and Foster 2008a; Smith and Foster 2008b). Glucose ingestion was not observed to significantly influence response accuracy in the present study. However it may be that the relatively small sample size, while adequate in terms of observing ERP differences between the two treatment conditions, was not sufficiently large to detect differences in response accuracy.

One further limitation of the present study is that participants were required only to fast for two hours prior to the testing sessions, whereas other studies in this area have typically incorporated an overnight fasting regimen. A previous study has specifically investigated the question of whether a glucose load preferentially modulates memory performance following an overnight fast relative to a two hour fast, as incorporated into the present study (Sünram-Lea *et al.* 2001). This previous study found evidence that glucose enhanced verbal episodic memory and recognition memory performance after an overnight fast and also after a two hour fast. Moreover, this study also demonstrated the glucose memory facilitation effect independent of whether testing took place in the morning or in the afternoon (Sünram-Lea *et al.* 2001). Therefore, on the basis of these previous findings it appears unlikely that the two hour fasting regime employed in the present study would have

substantially influenced the findings reported here. Indeed, it has been argued that the implementation of a two hour fast is desirable, given that such a fasting regimen represents optimal ecological validity in the context of investigating glucose modulation of memory with respect to real world functioning (Sünram-Lea *et al.* 2001).

In summary, the present study investigated the influence of acute glucose ingestion on ERP components mediated by recognition memory judgements that are differentially mediated by recollection and familiarity mechanisms in healthy adolescents. Glucose ingestion was associated with faster response times during the recognition memory task relative to placebo. Further, glucose ingestion was associated with an enhanced LP effect (an ERP marker of recollection) and an enhanced FN400 ERP effect (known to reflect familiarity). Taken together these findings a) support previous observations that oral glucose ingestion facilitates memory performance (in terms of response times) in healthy adolescents (Smith and Foster 2008a; Smith and Foster 2008b), and b) suggest that glucose administration facilitates both recollection and familiarity based recognition memory performance. These findings question the validity of the 'hippocampus hypothesis' pertaining to glucose modulation of memory, and suggest that glucose targets more global cortical regions in exerting a facilitatory effect on human cognitive performance.

Acknowledgements

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Table 1

The study procedure (the time in minutes of each procedure prior/subsequent to treatment delivery is displayed in the left column)

t (mins)	Procedure
-40	Preparation for EEG recording
-10	Baseline blood glucose measurement
0	Treatment administration
10	Blood glucose measurement
15	Recognition memory task
43	Final blood glucose measurement

Figure Captions

Figure 1

Blood glucose concentrations for the glucose and placebo conditions.

Figure 2

Grand average ERP old [correct] – new [correct] difference waveforms for frontal sites F3,

Fz and F4. Waveforms are displayed for the glucose and the placebo condition. The FN400

component is indicated.

Figure 3

Grand average ERP old [correct] – new [correct] difference waveforms for parietal sites P3,

Pz and P4. Waveforms are displayed for the glucose and the placebo condition. The LP

component is indicated.

Figure 4

Mean amplitude differences between the old [correct] and new [correct] conditions

subsequent to ingestion of the glucose and placebo treatments. The FN400 component

reflects the mean amplitude differences across the 300-500 ms latency range collapsed across

frontal scalp sites F3, Fz and F4. The LP component reflects the mean amplitude differences

across the 400-800 ms latency range collapsed across parietal scalp sites P3, Pz and P4.
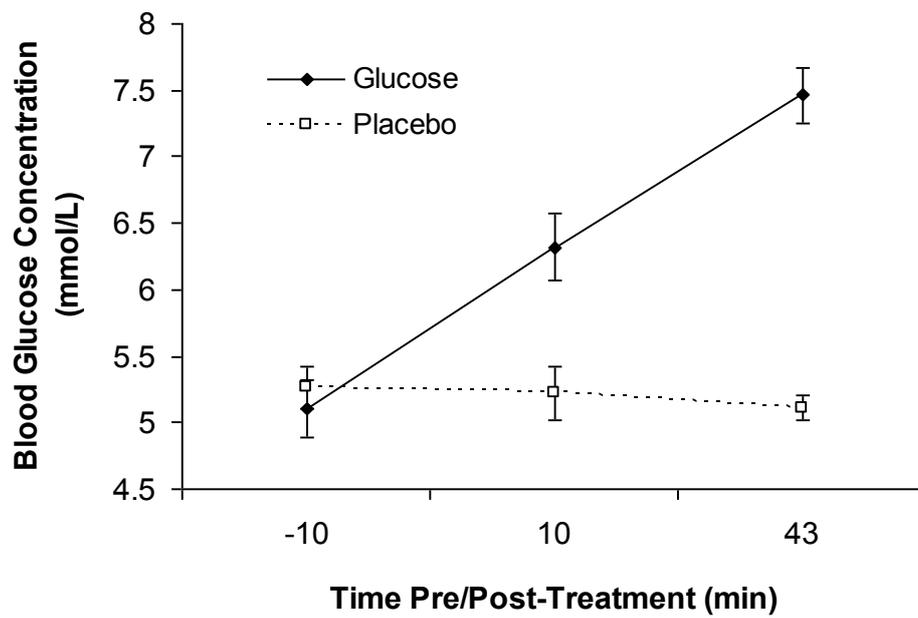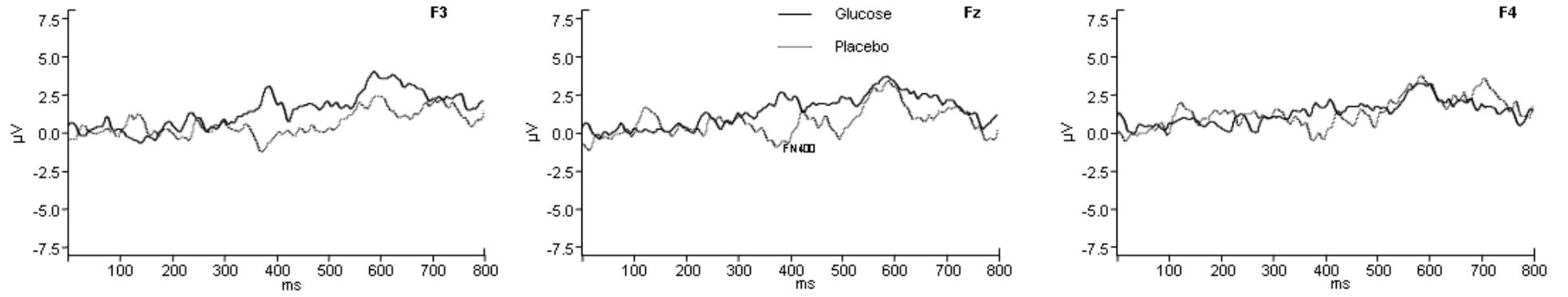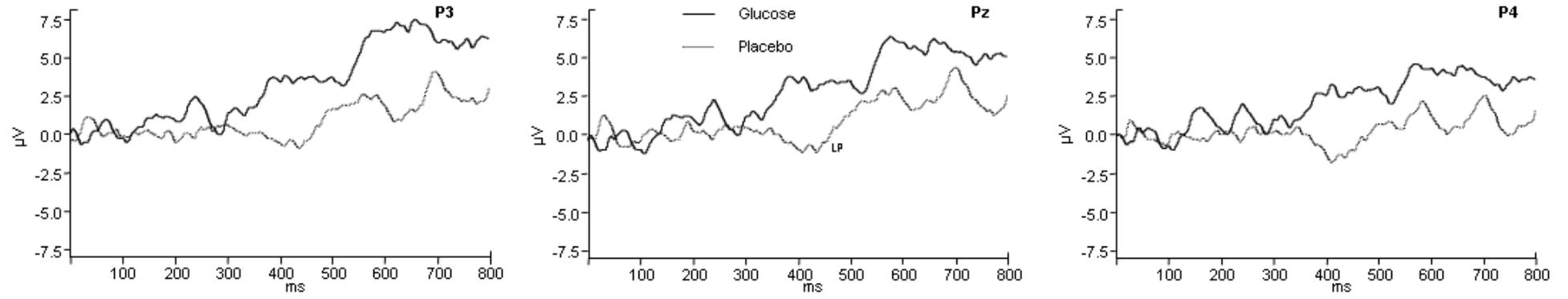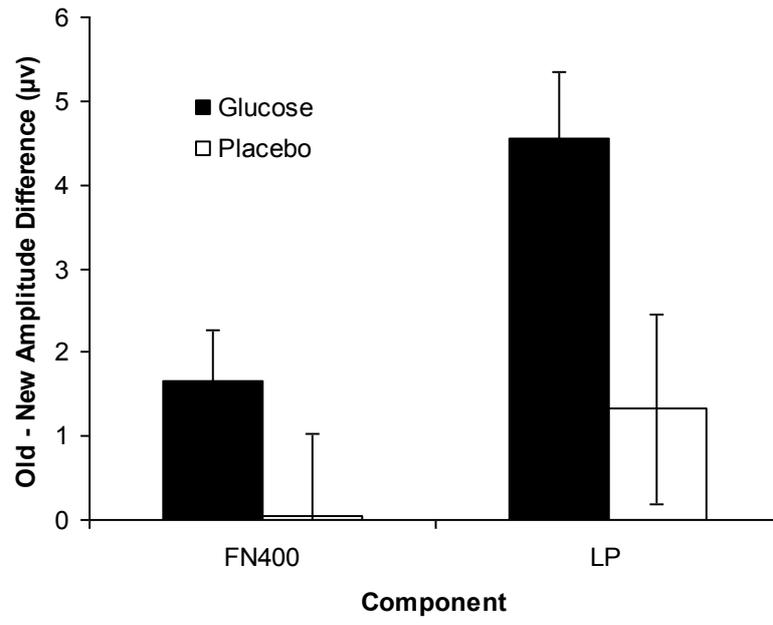
Figure 1

Figure 2

Figure 3

Figure 4