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# Glucose regulation and face recognition deficits in older adults: the role of attention

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## **Abstract**

The present study investigated the perceptual, attentional and memory processes underlying face recognition deficits observed in older adults with impaired gluoregulation. Participants were categorised as good gluoregulators or poor gluoregulators on the basis of an oral glucose tolerance test (OGTT). Using event-related potential (ERP) methodology, 23 participants (18 females, range = 62 to 88 years old, mean age = 73.87 years old, SD = 8.41) performed a 2-stimulus oddball task. Participants were asked to rate and memorise 10 ‘target’ faces, which were then presented amongst 120 unfamiliar foils. Behavioural results indicated that good gluoregulators were significantly more accurate at recognising target faces. ERP markers of early visual perception (the P1 and N170 components) and memory formation (the P3 component) were unaffected by gluoregulatory efficiency. The P2 component, an index of attentional processing, was larger and delayed in the poor gluoregulators. To the best of our knowledge, the present study is the first to suggest that face recognition deficits in poor gluoregulators may be due to impairments in attentional processing.

Key words: event-related potentials, gluoregulation, oddball paradigm, face recognition, ageing

## **Introduction**

Impairments in glucoregulation are associated with cognitive deficits in older adults (Meikle, Riby & Stollery, 2004; Messier, 2005; Riby et al., 2009; Riby & Riby, 2006). These deficits are observable in individuals with chronically impaired glucoregulation (e.g. Jones, Riby & Smith, 2016) and impaired glucose tolerance (e.g. Vanhanen et al., 1998). Cognitive impairment has also been demonstrated in healthy older adults with relatively poorer glucose regulation (i.e. individuals who demonstrate no overt signs of diabetes but have an increased blood glucose level in response to an oral glucose tolerance test; e.g. Messier, Tsiakas, Gagnon, Desrochers & Awad, 2003; Messier, Tsiakas, Gagnon, & Desrochers, 2010). Deficits are frequently observed in a number of cognitive domains including executive functioning, information processing and verbal episodic memory (Manschot et al, 2007; Yeung, Fischer & Dixon, 2009; Smith et al., 2014; Jones, Riby, Mitchell & Smith, 2014). Hyperglycaemia has been purported as a mechanism underpinning the link between impaired glucoregulation and cognitive deficits (Strachan, Reynolds, Marioni & Price, 2011). The development of type 2 diabetes has been shown to increase in healthy adults with increasingly poor glucoregulatory efficiency, even when this occurs within normal glucose tolerance limits (Levitan, Song, For & Liu, 2004). This suggests that progression of glucoregulatory problems occurs on a continuum and as such, investigating changes within a healthy population may shed light on the possible mechanisms underlying cognitive impairment in individuals with clinical impairments in glucoregulatory efficiency.

Memory problems induced by impaired glucoregulatory efficiency are more typically seen in the verbal domain (Lamport, Lawton, Mansfield & Dye, 2009), with very little research considering nonverbal memory (Messier, 2005). Further, there has been limited consideration of links to cognitive visual perceptual mechanisms beyond the physically detrimental impact of diabetic retinopathy (Ding et al., 2010). However, there is evidence in

the extant literature which suggests that poor glucoregulation impacts on face recognition ability (Zaslavsky, Gross, Chaves & Machado, 1995; Fontbonne, Berr, Ducimetière, & Alperovitch, 2001; Jones et al., 2016). Indeed, Fontbonne and colleagues (2001) investigated cognitive function in older adults i) with type 2 diabetes (DM2), ii) individuals with impaired fasting glucose (IFG) levels, and iii) healthy controls, over a four-year period. They found that DM2 participants performed similarly to IFG and control participants at baseline but their performance deteriorated to a significantly greater extent on a number of measures, including face recognition, after the four year follow up. Reduced connectivity between the hippocampus and surrounding regions has been reported in those with DM2, and previous research suggests that a disruption in connectivity between the fusiform face area and the hippocampus could explain these face recognition deficits (Zhou et al., 2010). Further, it has been suggested that administration of glucose enhances face recognition performance in young adults and in Alzheimer's patients (Manning, Ragozzino & Gold, 1993; Metzger & Flint Jr., 2003). This suggests that neural areas important to face recognition may be sensitive to impairments in glucose tolerance.

The event-related potential (ERP) technique provides a methodology for assessing cognitive performance in situations where overt behavioural responses cannot be reliably obtained, and is very useful for investigating the train of perceptual and neurocognitive processes engaged during an activity (see influential volume by Luck, 2014). Although ERPs have not been employed in the ageing literature to investigate glucoregulatory mediated face processing ability, ERPs have been used previously to investigate both glucoregulatory influences on cognition and neurocognitive mechanisms underpinning face processing (e.g. Hissa, D'Almeida, Cremasco, & de Bruin, 2002; Wiese, Komes & Schweinberger, 2012). The ageing literature therefore provides a useful foundation on which to base our investigation, particularly given the established relationship between cognitive performance,

glucoregulation and ageing (Lamport et al., 2009). Here we focus on the P1, N170, P2 and P3 components, which have been used consistently as biological markers of early perceptual, attention and memory processes elicited during face recognition in an elderly population (Cooray et al., 2011; Daniel & Bentin, 2012; Gao et al., 2009).

The P1 is the first positive ERP component associated with early visual perceptual processing that peaks approximately 100 ms post-stimulus onset. This component is sensitive to a number of early visual perception inputs including stimuli luminance and contrast and is elicited at scalp sites around the occipital region (Gao et al, 2009). While this component is not specifically associated with face processing (Rossion & Jacques, 2008), some studies have suggested that faces elicit a larger P1 component than non-face stimuli (e.g. Rossion & Caharel, 2011). Older adults are known to exhibit relatively larger P1 amplitudes and delayed P1 latencies relative to younger adults suggesting that this component becomes larger in amplitude and delayed in latency with cognitive deterioration in ageing (Gao et al., 2009). The most robust and frequently reported ERP component in face processing and recognition research is the N170 (Rossion & Jacques, 2008). This is a negative, early perceptual ERP component, peaking around 170 ms after stimulus onset, observed at occipito-temporal scalp sites, with higher amplitudes predominantly found for faces than other types of stimuli (Itier & Taylor, 2004). Evidence suggests it is face-sensitive and is related to the detection of structural features and configurations of the stimuli engaged prior to identification (Wiese, Schweinberger & Hansen, 2008; Rossion & Jacques, 2008 for a review). The P2 component is a positive going deflection that usually follows the N170 component in face recognition tasks (Wolff, Wiese & Schweinberger, 2012), peaking approximately 200 ms post-stimulus onset over occipito-parietal and temporal sites. This component is considered to reflect processes of perceptual and configural processing to enable subsequent face recognition (Latinus & Taylor, 2006; Zheng, Mondloch & Segolowitz, 2012). Smaller P2 amplitudes are

associated with relatively better face recognition (Zheng et al., 2012), suggesting that amplitudes may be larger in individuals with poor face recognition ability. A similar component has been observed in oddball tasks but over frontal and central electrode sites (Riby et al, 2008). This component is associated with higher level perceptual and attentional processing, particularly of visual stimuli, with increased amplitudes in response to repeated stimuli compared to novel stimuli (Curran & Dien, 2003; Luck & Hillyard, 1994; Evans & Federmeier, 2007; Riby et al., 2008). Impairments in attentional processing have been reported in relatively healthy older adults with an increased risk for type 2 diabetes (Vanhanen et al., 1997). Speculatively, impairments in attentional processing could be a mechanism underpinning the face recognition deficits associated with impaired gluco-regulation. A further component that has been investigated in relation to both face recognition, and gluco-regulation is the P3. This component is a positive deflection, observed at central frontal and parietal scalp sites, peaking approximately 300-350 ms post-stimulus onset and often comprising two subcomponents depending on the paradigm: P3a (associated with executive function and automatic orientation of attention to task irrelevant stimuli) and the P3b (associated with memory updating and formation of memory representations; Polich, 2007). As the present study is focussed on the recognition (and therefore, memory) of faces, we are specifically interested only in the P3b component, which will be referred to herein as the P3. The P3 component is evoked by the oddball task, which measures sustained attention and identification of infrequently presented stimuli, and is maximal over frontal and central electrode sites (Polich, 2007). The investigation of this component in gluco-regulation research has revealed that P3 latencies are significantly delayed and longer during an auditory oddball tasks in DM2 participants relative to healthy controls (Cooray et al., 2011; Hissa et al., 2002). The longer latencies observed may reflect delayed memory processing and consequently deficits in memory updating and formation in DM2 (Polich, 2007).

The preliminary findings demonstrate a clear association between impaired glucoregulatory efficiency and face recognition deficits (Zaslavsky et al., 1995; Fontbonne et al., 2001; Jones et al., 2016) and in conjunction with findings that face recognition declines as part of the normal ageing process (e.g. Boutet & Faubert, 2006; Lott, Haegerstrom-Portnoy, Schneck, & Brabyn, 2005) suggest that it is timely to investigate further i) whether impaired glucoregulatory efficiency in older adults is associated with face recognition deficits, and ii) the neurocognitive mechanisms associated with such deficits. That is, does impaired glucoregulation impact specifically upon such processes as i) general visual perception, ii) visual perception specific to faces, iii) attentional processing, iv) memory updating and formation, or v) a combination of these factors, with these deficits emerging as overt face recognition deficits in behavioural paradigms? The aim of the present study was to systematically investigate this question, by employing the temporal precision of ERP methodology. There were a number of specific predictions. First, if face recognition deficits observed in those with poor glucoregulation are due to inefficiency in early perceptual processing, the overall P1 and N170 amplitudes would be larger and their latencies longer in those with poor glucoregulation relative to those with good glucoregulation. Speculatively, ERP components affected by ageing may be more amenable and hence sensitive to impairments in glucoregulation, given that a relationship between glucoregulation, cognition and ageing has been suggested (Lamport et al., 2009). Secondly, if attention is critical to the observed deficits, it was predicted that the P2 amplitudes and latencies of poor glucoregulators would be significantly larger and delayed compared to good glucoregulators. Finally, if memory deficits underpin impaired face recognition performance in poorer glucoregulators, then predicated by Cooray and colleagues (2011), it was hypothesised that the latency of the P3 to infrequent target faces would be delayed in participants with poor glucoregulation compared to those with good glucoregulation.



## **Method**

### ***Participants***

Twenty-three participants aged 60 years and over took part (18 females, range = 62 to 88 years old, mean age = 73.87 years old, SD = 8.41). The following exclusion criteria applied to all participants; participants were excluded if they: were under 60 years of age; were left-handed; were not proficient in English; were suffering from any serious medical (i.e. coronary disease, diabetes, asthma) or psychiatric condition (i.e. depression, anxiety related disorders) at the time of testing; had a diagnosis of dementia or memory disorder (e.g. mild cognitive impairment); were suffering from any acute viral infection (i.e. cold / flu) at the time of testing; had any learning difficulties or dyslexia; had a history of brain injury; had a diagnosis of diabetes (Type 1 or Type 2), or other metabolic conditions which impact upon glucose regulation; had a visual impairment that could not be corrected with glasses or contact lenses; had any known active infections; were HIV antibody positive or thought they may be HIV positive; had at the time of testing, have ever had, or thought they may be at risk of hepatitis; had jaundice in the year prior to testing; had breast cancer and/or a mastectomy; had haemophilia or any similar blood clotting disorder. Participants were also excluded if their fasting blood glucose level exceeded 6.1 mmol/l.

Participants were recruited from an older adult participant database held at Northumbria University, as well as through local older adult groups and newsletters. Participants were given £15 as compensation for their time and out-of-pocket expenses. Written informed consent was obtained from all participants prior to testing. Ethical approval was obtained from the School of Life Sciences ethics committee at Northumbria University.

Participants were split into two groups based on their area-under-curve (AUC) measurements on the oral glucose tolerance test (OGTT), categorised by median split into 11 ‘poor’ and 12 ‘good’ gluco regulators. Table 1 shows the descriptive statistics for each group. The mean blood glucose levels at each time point across the two-hour period are shown for each gluco regulatory group in Figure 1. No significant differences were observed between the two groups in terms of age, BMI, National Adult Reading Test (NART) scores, Mini Mental State Examination (MMSE) scores or baseline fasting glucose levels. There was a significant difference between good and poor gluco regulators in terms of gluco regulation (AUC) and two-hour post-glucose load blood glucose levels; poor gluco regulators had significantly higher values than good gluco regulators. In line with the WHO guidelines, both groups of participants had fasting blood glucose levels considered to be normoglycemic but the poor gluco regulation group had a mean two-hour post glucose load levels that is indicative of impaired glucose tolerance (IGT).

INSERT TABLE 1 AND FIGURE 1 ABOUT HERE

### *Stimuli*

The oddball task was presented using E-Prime software (E-Prime 2.0, Psychology Software Tools) on a Windows desktop PC. Face stimuli were obtained from the Glasgow Unfamiliar Face Database (Glasgow University, UK; Burton, White & McNeill, 2010). They were presented in the centre of the screen against a white background, standardised to a height of 314 pixels, with a width between 209 and 251 pixels. The oddball task comprised

two test blocks in which ten infrequent target faces and 240 frequent non-target faces were presented. The ten target faces were selected at random; five male faces and five female faces. One hundred and twenty faces were selected for each test block (240 faces in total); 60 randomly selected female faces and 60 randomly selected male faces.

### ***Materials***

*OGTT and blood glucose monitoring equipment.* Participants fasted overnight before completing an OGTT the next morning. Baseline blood glucose levels were measured by taking capillary blood drawn from the fingertip using Accu-Chek Safe-T-Pro Plus lancets. One drop of capillary blood was applied to an Optium Plus glucose reagent strip (Abbott Diabetes Care Ltd, Oxford, UK) for blood glucose quantification using an Optium Xceed glucometer (Abbott Diabetes Care Ltd, Oxford, UK). According to the manufacturer, this device has acceptable reliability (coefficient of variation = 3.8-5.2%) and validity (correlation between the Optium Xceed and a laboratory reference method is  $r = 0.97$ ). Participants were then allowed 10 minutes to drink a solution of 75g of glucose, 200 ml of water and 30 ml of no-added sugar orange squash. Participant blood glucose levels were then measured 30 minutes, 60 minutes, 90 minutes and 120 minutes post-ingestion. Following blood glucose measurements, participants were provided with a choice of cereal and semi-skimmed milk for breakfast. AUC was calculated with respect to ground (Smith & Foster, 2008; Sünram-Lea, Owen, Finnegan & Hu, 2010), taking into account participant fasting levels and thus considering total output. The following calculation was used:  $[(BGC_{30}-FGC)/2] \times (30-0) + [((BGC_{30}-FGC)+(BGC_{60}-BGC_{30}))/2] \times (60-30) + [((BGC_{60}-FGC)+(BGC_{90}-FGC))/2] \times (90-30) + [((BGC_{90}-FGC) + (BGC_{120}-FGC))/2] \times (120-90)$  (FGC = fasting glucose

concentration; BGC is blood glucose concentration at that time point in minutes e.g. BGC30 = blood glucose concentration after 30 minutes).

*National Adult Reading Test.* This is a brief vocabulary test that is used as a measure of premorbid intellectual ability. Participants read 50 words with irregular grapheme-phoneme correspondence aloud (Coltheart, Patterson & Marshall, 1987) and are given a point for each word pronounced correctly according to English language conventions. The total score is used as a premorbid IQ estimate.

*Mini-mental State Examination.* This test is a standardised tool used to screen for dementia as it allows a global assessment of any cognitive deficits. Participants are considered to have normal cognition if their score is equal to or higher than 25 out of 30; mild cognitive impairment if they score 21-24; moderate cognitive impairment if they score 10-20 and severe cognitive impairment if their score is 9 or below.

*Familiarisation and the Oddball task.* Participants were initially presented with 10 target faces on a computer screen and asked to rate them on 9 scales by circling their answer on the paper questionnaire [distinctiveness, attractiveness, friendliness, approachability, honesty, trustworthiness, age, confidence, intelligence] (Osborne & Stevenage, 2013). They made these ratings three times in order for participants to familiarise themselves with the faces. Each face was presented for 5000 ms, allowing enough time to rate and memorise the face. After a five-minute interval, participants then completed an oddball task. The oddball task comprised two blocks separated by a two-minute interval. Within each block there were 150 randomly presented faces: the ten target faces were presented three times each amongst 120 previously unseen faces. A fixation cross was presented for 500 milliseconds (ms) followed by the stimulus for 1000 ms, and then a blank screen for 1000 ms. Participants were instructed to press the space bar on the keyboard every time they saw one of the ten faces they had seen and rated previously.

### ***EEG/ERP recording and data reduction***

EEG was recorded with a 32-channel electrode cap (BioSemi Active Two), fitted with silver/silver chloride active electrodes based on an extended 10-20 system (Jasper, 1958; American Electroencephalographic Society, 1994). Electroconductive gel was used to maintain contact between the electrodes and scalp surface. The montage included four midline sites (Fz, Cz, Pz and Oz), 14 sites over the left hemisphere (Fp1, AF3, F3, F7, FC1, FC5, C3, T7, CP1, CP5, P3, P7, PO3 and O1) and 14 sites over the right hemisphere (Fp2, AF4, F4, F8, FC2, FC6, C4, T8, CP2, CP6, P4, P8, PO4 and O2). The EEG signal was referenced to linked electrodes placed on the mastoids which were digitised at a rate of 2048 per second. Vertical electro-oculogram was recorded via the placement of electrodes approximately 1 cm above and 1 cm below the left eye.

EEG epochs recorded from 200 ms pre-stimulus onset to 1000 ms post-stimulus onset were extracted for averaging. Automatic ocular artefact correction, EEG signal band-pass-filtering at 0.46-30 Hz, artefact rejection (for trials where ERPs extended beyond the range of -75 to 75  $\mu$  V for any channel) and ERP averaging were conducted offline using Edit 4.5 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.

EEG data was discarded from two participants due to insufficient artefact-free trials across each of the critical averages for the test session. A further four participants had insufficient artefact-free trials in the infrequent target condition. Therefore the total number of participants included in each of the grand averages (both infrequent target condition and

frequent non-target condition) was 17 overall; eight poor gluco regulators and nine good gluco regulators based on a median split of the area-under-the-curve measurements calculated from the participants' OGTT data. The exclusion of participants did not result in any new between group differences across health and demographic variables. After removing participants, no significant differences were found in age, BMI, NART, MMSE, baseline or two-hour post glucose levels (although this trended towards significance [ $p = .064$ ]) or in resting systolic and diastolic blood pressure. For the infrequent target condition, there were a mean number of 41 artefact-free trials for good gluco regulators and 45 artefact-free trials for poor gluco regulators. For the frequent non-target condition, there were a mean number of 134 artefact-free trials for the good gluco regulators and 170 artefact-free trials for the poor gluco regulators.

### ***Procedure***

Participants attended two sessions (the interval between sessions was no longer than two weeks). In the first session, participants fasted overnight (at least 12 hours) before completing an OGTT in the morning in the lab. They completed the National Adult Reading test (Coltheart, Patterson & Marshall, 1987), the Mini Mental State examination (Folstein, Folsten & McHugh, 1975), and their height and weight were recorded.

In the second session, participants completed the oddball task while EEG was simultaneously recorded. Participants were instructed to remain relaxed and as still as possible and to keep their eyes on the screen to minimise movement-related EEG artefacts. After completing the tasks, participants were debriefed and given the opportunity to ask any questions about the experiment.

### *Design and analysis*

A mixed design was used, with one between-subjects and one within-subjects factor. The between-subjects factor was glucoregulation group (2 levels: poor and good). The within-subjects factor was stimulus type (2 levels: infrequent target and frequent foil). All analyses were Bonferroni-corrected.

Accuracy was measured by first converting each participant's score into a percentage of correct hits and false alarms. The percentage of false alarms was then subtracted from the percentage of hits to give a measurement of accuracy. Reaction time was the mean time taken by the participants to correctly identify an infrequent target face in milliseconds.

ERP analyses were conducted for each of the four components P1, N170, P2, P3. The mean amplitude and peak latency for each component epoch was calculated for each participant. Targeted analyses comparing pairs of electrodes (one in each hemisphere against the other) was conducted in order to focus on specific regions related to specific processes rather than overall scalp locations. For the P1, N170 and P3 components, separate 2 (hemisphere: left and right hemisphere) x 2 (group: good vs. poor glucoregulation) x 2 (stimulus type: infrequent target vs. frequent foil) ANOVAs were run on the amplitude and latency data at selected electrode sites for each component. For the P2 component, separate 2 (group) x 2 (stimulus type) ANOVAs were run on the amplitude and latency data at selected electrode sites for each component. On visual inspection and predicated by the literature (Gao et al, 2009), there appeared to be a prominent difference between the groups at occipito-parietal sites at the P1 time region so these have been included in the analysis (i.e. O1, O2, PO3, PO4, P7 and P8). Past research has revealed that the N170 component has been

predominantly detected in the right parietal hemisphere at the P8 electrode during face processing tasks (Rossion & Jacques, 2008). However, the N170 has also been seen in the left hemisphere and due to the lack of laterality often observed in older adults (Chaby et al., 2001), data analysis was conducted on data from Pz, P7 and P8 electrodes. Previous research has indicated that the P2 component is centred around frontal and central scalp locations (Riby et al, 2008) therefore analysis was conducted on the data from the Fz and Cz electrodes. In contrast, the P3 component has been reported previously to be centred around central and parietal sites (Polich, 2007) therefore analysis of this component were based on the data from the CP1, CP2, Pz and Cz electrodes. For all ERP analyses only significant effects are reported in text.

## **Results**

### ***Behavioural results***

#### *Accuracy*

Based on the results of all 23 participants, an independent-samples t-test was run comparing the two groups. As Levene's test of equality of variances was significant [ $F = 16.59$ ,  $p = .001$ ], equal variances were not assumed, and therefore significance values which are corrected for non-homogeneity of variance are reported. A significant difference was found between the two groups [ $t(11.43) = 2.81$ ,  $p = .016$ ,  $d = 1.22$ ] whereby good glucoregulators [mean = 98.72 (SD = 2.08)] were significantly more accurate than poor glucoregulators [mean = 92.20 (SD = 7.43)].



### *Reaction time*

Again, based on the results of all 23 participants, an independent-samples t-test was run comparing the groups on their reaction time during the task. No significant difference in reaction time [ $t(21) = 0.93, p = .37, d = .39$ ] was found between the good gluco regulators [mean = 729.98 (SD = 60.99)] and the poor gluco regulators [mean = 703.93 (SD = 73.94)].

### *ERP results*

INSERT FIGURE 2 ABOUT HERE

#### *P1 component*

Figure 2 shows the grand average waveforms at P7, P8, PO3, PO4, O1 and O2. The mean amplitude and peak latency for the P1 component were taken from the 130-165 ms latency range based on visual inspection and previous research (Gao et al., 2009). At occipital sites O1 and O2, the mean amplitude data trended towards a significant main effect of group ( $p = .051$ ), with good gluco regulators exhibiting larger mean amplitudes than poor gluco regulators. There was a significant main effect of hemisphere with peak latency observed to be significantly slower in the right hemisphere (O2) than in the left (O1) [ $F(1,15) = 8.07, MSE = 23.29, p = .012, \eta_p^2 = .35$ ].

INSERT FIGURE 3 ABOUT HERE

#### *N170 component*

On the basis of previous research (Chaby et al., 2001; Gao et al., 2009) and visual inspection, the mean amplitude and peak latency for the N170 component were taken from the 170-235 ms latency range (Figure 3). The peak latency analysis at electrode sites P7 and P8 revealed that there was a significant main effect of stimulus type, whereby there was a significantly delayed peak latency for frequent foil stimuli compared to infrequent target stimuli [ $F(1,15) = 5.80$ ,  $MSE = 27.63$ ,  $p = .029$ ,  $\eta_p^2 = .28$ ].

INSERT FIGURE 4 ABOUT HERE

### *P2 component*

Figure 4 shows the grand average waveforms at Fz and Cz. The mean amplitude and peak latency for the P2 component were taken from the 180-265 ms latency range based on previous research and visual inspection (Riby et al., 2008). The amplitude analysis revealed that at Fz there was a significant main effect of group, with poor gluco regulators exhibiting a larger mean amplitude than those with good gluco regulation [ $F(1,15) = 4.72$ ,  $MSE = 9.48$ ,  $p = .042$ ,  $\eta_p^2 = .25$ ]. For peak latency, at Fz there was a significant main effect of group, whereby participants with poor gluco regulation had a significantly delayed peak latency than those with good gluco regulation [ $F(1,15) = 5.11$ ,  $MSE = 446.55$ ,  $p = .039$ ,  $\eta_p^2 = .25$ ].

INSERT FIGURE 5 ABOUT HERE

### *P3 component*

The mean amplitude and peak latency for the P3 component (Figure 5) were taken from the 545-780 ms latency range based on visual inspection of the data and in line with previous research (Daniel & Bentin, 2012). For peak latency, there was a significant three-way interaction between hemisphere, stimulus type and group at sites CP1 and CP2 [ $F(1, 15) = 6.30$ ,  $MSE = 273.41$ ,  $p = .024$ ,  $\eta_p^2 = .30$ ]. Post-hoc analysis revealed that for participants with poor glucoregulation, there were no significant main effects of hemisphere or stimulus type and no significant interaction was found. However, participants with good glucoregulation showed no significant main effects of hemisphere or stimulus type but a significant interaction between hemisphere and stimulus type [ $F(1, 8) = 6.78$ ,  $MSE = 334.14$ ,  $p = .031$ ,  $\eta_p^2 = .46$ ] was observed; the difference between target and foil stimuli latency at CP1 approached significance ( $p = .057$ ), with peak latency slower for target than for foil stimuli.

### ***ERPs and behaviour***

#### *P1 component*

Overall, no significant correlations between behavioural performance and i) mean amplitude or ii) peak latencies across any of the electrodes were observed. This result held when each glucoregulatory group was analysed separately.

#### *N170 component*

Table 2 shows the correlations between the N170 mean amplitude and peak latencies with behavioural accuracy and hits. In terms of peak latency, at P7, accuracy was

significantly negatively associated for both infrequent target faces and frequent non-target faces ( $p = .03$  and  $p = .009$  respectively). The number of hits was also significantly negatively associated with frequent non-target stimulus peak latency ( $p = .012$ ). At P8, both accuracy and number of hits were negatively correlated with the non-target faces ( $p = .011$  and  $p = .024$  respectively).

For good glucoregulators, the N170 latency data indicated peak latency for target stimuli at electrode site P7 was significantly negatively correlated with both number of hits ( $p = .04$ ) and accuracy ( $p = .02$ ). Peak latency for non-target faces was also significantly negatively correlated with both number of hits ( $p = .047$ ) and accuracy ( $p = .048$ ).

INSERT TABLE 2 ABOUT HERE

### *P2 component*

As indicated by Table 3, the peak latencies observed for target and non-target faces at Fz and Cz were all significantly negatively correlated with both accuracy and number of hits.

For poor glucoregulators, the P2 latency data revealed that peak latency for targets at electrode site Cz was significantly negatively associated with both number of hits ( $p = .04$ ) and accuracy ( $p = .02$ ).

INSERT TABLE 3 ABOUT HERE

### *P3 component*

Table 4 shows the overall correlations between behavioural performance, mean amplitude and peak latencies of the P3 component. For peak latency, at CP1, both accuracy and number of hits were significantly negatively associated with P3 peak latency ( $p = .006$  and  $p = .02$  respectively). At CP2, accuracy was also significantly negatively correlated with P3 peak latency ( $p = .04$ ).

For good glucoregulators, peak latency for target stimuli at electrode sites Pz and Cz were both significantly correlated with accuracy ( $p = .05$  and  $p = .02$  respectively). Peak latency for frequent non-target foils were significantly negatively correlated with accuracy at electrode sites CP1 ( $p = .03$ ), Pz ( $p = .001$ ), and CP2 ( $p = .02$ ). Peak latency for non-targets was also significantly negatively correlated with number of hits at electrode sites Pz ( $p = .001$ ) and CP2 ( $p = .03$ ). For poor glucoregulators, there was a significant positive correlation between the number of hits and mean amplitude for non-targets at electrode site Cz ( $p = .04$ ). In terms of peak latency, there were significant negative associations between peak latency for non-targets at electrode site CP1, and number of hits ( $p = .04$ ), as well as accuracy ( $p = .04$ ).

INSERT TABLE 4 ABOUT HERE

## **Discussion**

The aim of the current study was to investigate further the neurocognitive mechanisms underpinning face recognition deficits in older adults with compromised gluco-regulatory efficiency. This was achieved by moving beyond behavioural methods alone and tracking ERPs during a 2-stimulus oddball task. The behavioural results indicated that those with good gluco-regulation were significantly more accurate at recognising the ten target (familiar) faces compared to those with poor gluco-regulation. This finding is aligned with previous work which has observed face recognition deficits in individuals with compromised gluco-regulatory efficiency (Zaslavsky et al., 1995; Fontbonne et al., 2001; Jones et al., 2016). However, the primary concern here was using the temporal precision of ERPs to uncover the specific mechanisms impaired during the task, which may account for face recognition deficits.

Perhaps the most noteworthy ERP finding observed was that poor gluco-regulators exhibited significantly greater mean amplitudes and delayed peak latencies than good gluco-regulators at midline frontal sites. The correlational data further indicates that peak latency was significantly associated with behavioural performance: for target stimuli at electrode site Cz, delayed peak latency was associated with poorer behavioural performance (number of hits and accuracy). In oddball tasks, the P2 component is considered to index attentional processing of stimuli (Riby et al., 2008) and in face processing has been found to be reduced and delayed in older adults (Wolff et al., 2012). Further, the P2 component has been associated with early individuation and thus identification of faces (Zheng et al., 2012) and may therefore reflect attention to and identification encoding of a face. At occipito-parietal sites, smaller P2 amplitudes have been found to correlate with stronger identification

of faces (Zheng et al., 2012). The present study findings align with a previous behavioural finding in which older adults with DM2 exhibited relatively poor performance on a face recognition task which relies predominantly on attentional as opposed to memory processing (Fontbonne et al., 2001). Consequently, these findings suggest that face recognition deficits observed in poor glucoregulators may be a consequence of impaired attentional processing requiring more effort to process/encode faces.

Previous investigations of the effects of ageing on face processing and recognition have indicated that older adults exhibit larger P1 and N170 amplitudes when presented with face stimuli compared to young adults (Gao et al., 2009). Therefore, based on the notion that poorer glucoregulatory efficiency in older age is an index of cognitive decline (Meikle et al., 2004), it was predicted that poor glucoregulators would exhibit larger and delayed P1 and N170 amplitudes than good glucoregulators. However, the results of the current study revealed no difference in P1 and N170 amplitude or latency between the two groups. This finding is consistent with a previous report that alterations in glucose metabolism do not affect the P1 component (Seaquist et al., 2007). The correlational data also indicated minimal significant associations between the P1 and N170 mean amplitudes with behavioural performance. Taken together, these findings suggest that face recognition deficits in older adults with compromised glucoregulatory efficiency are not accounted for by impaired perceptual processing, nor early face perceptual processes.

It was predicted that participants with poor glucoregulation would have delayed P3 latencies relative to good glucoregulators. However, the results presented here revealed no differences in amplitude or latency between the two glucoregulatory groups. This contradicts previous research that has found differences in P3 latency between adults with DM2 and healthy controls (Cooray et al., 2011; Hissa et al., 2002) and suggests that face recognition deficits in poor glucoregulators are not modulated by memory updating. A major difference

between the present study and previous studies which have observed delayed P3 latencies in individuals with DM2 is that the previous work used auditory memory paradigms; thus this effect may not hold when stimuli is presented visually as was the case here. Equally, the effect may not be present in individuals who do not have chronically impaired glucose tolerance. In terms of correlations between the P3 component and behavioural performance, it was evident in both groups that delayed peak latency equated to poorer accuracy on the face recognition task. There was also some evidence to suggest an increase in P3 amplitude with better behavioural performance. These correlations indicate a possible relationship between the P3 component and face recognition performance, similar to that observed for the P2 component. However, this was not moderated by glucoregulatory efficiency. On this basis, it seems appropriate to speculate that face recognition deficits in older adults with relatively poorer glucoregulatory efficiency may be underpinned by impairments in attentional mechanisms as opposed to memory processes. This is a novel finding that has not been previously considered in the literature.

The underlying physiological mechanisms that are responsible for the observed cognitive impairments have yet to be elucidated, but several possible mechanisms have been proposed. These include hyperglycaemia, hypertension and hypothalamic-pituitary-adrenal (HPA) axis dysregulation (Strachan, Reynolds, Marioni & Price, 2011). The most pertinent mechanism in the current study is hyperglycaemia, as a result of increased insulin resistance and/or decreased insulin sensitivity. An association has been reported between insulin resistance, cognitive impairment and reduced brain size in middle-aged and older adults (Baker et al., 2011; Benedict et al., 2012; Tan et al., 2011), and desensitisation of insulin receptors within the brain have been suggested to play a role in Alzheimer's Disease (Hoyer, 2002). Thus, deterioration of brain insulin signalling may potentially explain the cognitive impairment experienced by individuals with poor glucose regulation (Kravitz, Schmeidler &



Beeri, 2013). It has been suggested that the increased blood glucose concentration that results from hyperglycaemia causes alterations in regional cerebral blood flow and may also cause changes to endothelial cells within the brain (Strachan et al., 2011). Speculatively, the observed impairments in attentional mechanisms in the current study may be caused by disruptions in uptake of glucose within the fronto-parietal network, where visual attentional processing is considered to take place (Kanwisher & Wojciulik, 2000). Another potential mechanism that has been linked to cognitive decline in individuals with poor glucoregulatory efficiency is hypertension (van den Berg, Kloppenberg, Kessels, Kappelle, & Biessels, 2009). Increases in blood pressure have been associated with atrophy in frontal brain regions in individuals with DM2 (Sakurai et al., 2006) and given the relatively high mean baseline blood pressures of the participants within the current study, this may explain the observed impairments in attentional processing. Initial damage as a result of comorbid hypertension to the frontal lobes may result in both the behavioural and ERP observations of the current study. HPA axis dysregulation, resulting in increased levels of cortisol within the bloodstream, has been suggested as another potential explanation of cognitive decline in individuals with poor glucoregulatory efficiency (Strachan et al., 2011). For example, in patients with DM2, high morning cortisol levels have been associated with cognitive impairment (Reynolds et al., 2010). Considering that the present study investigated cognitive performance in terms of memory accuracy (relating to the oddball face), future research could include the investigation of cortisol levels as a potential factor, particularly given that exposure of the hippocampus to glucocorticoids has been associated with cognitive decline in ageing (McEwen, 1999).

A number of limitations must be considered. One limitation that should be noted is that the sample size is small, however the sample size was comparable with previous similar studies (e.g. Riby et al., 2008; Schultes et al., 2005; Smith et al., 2009). Further, while the use

of the median split to divide participants within this study into poor and good glucoregulators is a feature of previous studies in this area (Messier et al., 2011; Messier et al., 2010; Messier, Tsiakas, Gagnon, Desrochers & Awad, 2003), glucose tolerance is considered to be a continuum and therefore dichotomising this variable may lead to an increased risk of type 1 error (Austin & Brunner, 2004; MacCullum, Zhang, Preacher & Rucker, 2002). Those participants who have OGTT AUC results that lie close to the median (whether below or above) may not vary drastically, particularly given that glucose regulation is likely to be reasonably normally distributed, thus the values of many participants will cluster around the median. A larger sample would have allowed a comparison of participants with and without clinically impaired glucose tolerance (in accordance with WHO guidelines). Future, larger studies could overcome this issue by making use of more sophisticated analysis techniques which require larger sample sizes, such as linear mixed modelling. It should also be noted that the age difference between the two glucoregulatory groups did approach significance ( $p = .10$ ) and thus ageing may have contributed to the observed differences in ERPs and behaviour. Considering that there is an established relationship between age, cognitive decline and impaired glucose tolerance (Lamport et. al, 2009), this difference is not surprising but future research should consider age-matching the groups more closely to rule this out as a contributing factor. Future research should look to control more appropriately for clinically relevant features of prediabetes and diabetes, including elevated blood pressure, waist circumference, triglycerides and reduced HDL-C. Nevertheless, given that these clinical features are part of the clinical profile of individuals with glucoregulatory problems, we did not want to exclude participants on this basis. A final limitation is that no nutritional restrictions were placed on participants prior to the second session and no data relating to glucose levels was retrieved from participants during this session. As such, the ingestion of carbohydrates and consumption of caffeine may have had an influence on the results. It is

typical of research in this area not to conduct an OGTT on the day of testing in order not to fatigue participants, and to rule out the influence of either fasting or a glucose load on task performance (e.g. Messier et al., 2003; Messier et al., 2010).

In summary, the present study investigated the influence of glucoregulation on face processing and recognition in healthy older adults using an ERP oddball paradigm, with the aim of identifying the neurocognitive mechanisms that underpin face recognition deficits in individuals with compromised glucoregulatory efficiency. To the best of our knowledge, this is the first study to systematically investigate the mechanisms underpinning the face recognition deficits associated with impaired glucose regulation. The findings indicated that glucoregulation did not appear to impact upon early visual processing (the P1 and N170 components) or memory updating/formation (the P3 component), but did appear to modulate attentional processing, specifically, early individuation and recognition of faces (the P2 component). It is important to note, that whilst the glucoregulatory indices of those participants with relatively poor glucoregulation reflected IGT, the results may not necessarily be extrapolated to those with chronically compromised glucoregulatory efficiency (i.e. DM2). Future work should aim to replicate these findings in individuals with DM2, given that face recognition deficits are a known feature of the DM2 cognitive profile (Jones et al., 2016). This is particularly important given that a decline in attentional processing capacity in DM2 may impact upon face recognition and other cognitive processes which are important for everyday functional living. Further, strategies could be put in place early to aid those with poor glucoregulation who suffer with face recognition deficits. By implementing strategies that aid with maintaining attention, such as cueing or focussing on internal facial features, deficits in face recognition may be alleviated. To conclude, the temporal resolution of the ERP technique employed in this study has enabled us to ascertain, for the first time, that compromised glucoregulatory efficiency potentially impacts upon structural encoding

and attentional mechanisms which are required to successfully recognise faces, but that later memory consolidation and earlier perceptual processes are unaffected by glucoregulatory status.

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**Table 1.** Participant characteristics (mean and SD)

	<b>Good glucoregulators (n=12)</b>	<b>Poor glucoregulators (n=11)</b>	<b><i>p</i></b>
<i>Age</i>	71.08 (7.59)	76.91 (8.53)	.10
<i>BMI</i>	26.89 (6.08)	26.56 (6.01)	.90
<i>NART</i>	37.83 (7.97)	41.55 (4.80)	.20
<i>MMSE</i>	28.08 (1.62)	28.09 (1.70)	.99
<i>AUC (mmol/l)</i>	429.88 (114.43)	825.14 (178.05)	<.001*
<i>Baseline fasting glucose level (mmol/l)</i>	5.03 (0.49)	5.13 (0.36)	.58
<i>Two-hour post glucose load level (mmol/l)</i>	6.39 (1.36)	8.65 (2.14)	.006*
<i>Resting systolic blood pressure (mmHg)</i>	134.27 (15.84)	138.09 (15.52)	.57
<i>Resting diastolic blood pressure (mmHg)</i>	83.27 (8.51)	74.64 (10.69)	.049*

\*indicates  $p < .05$

**Table 2.** Correlations between behavioural performance, and N170 mean amplitude and peak latency to targets and non-targets in good and poor glucoregulators.

			<b>P7</b>		<b>Pz</b>		<b>P8</b>	
			<b>target</b>	<b>non-target</b>	<b>target</b>	<b>non-target</b>	<b>target</b>	<b>non-target</b>
<i>N170 Amplitude</i>	<i>Good glucoregulators</i>	<i>Hits</i>	-.330	-.407	-.335	-.284	-.379	-.348
		<i>Accuracy</i>	-.524	-.611	-.355	-.355	-.486	-.496
	<i>Poor glucoregulators</i>	<i>Hits</i>	.461	.450	.206	.310	-.175	-.255
		<i>Accuracy</i>	.463	.407	.200	.293	-.260	-.349
	<i>Overall</i>	<i>Hits</i>	0.115	0.094	-0.033	0.059	-0.224	-0.24
		<i>Accuracy</i>	0.032	-0.016	-0.083	-0.006	-0.316	-0.337
<i>N170 Latency</i>	<i>Good glucoregulators</i>	<i>Hits</i>	-.696*	-.673*	-.039	.107	-.270	-.466
		<i>Accuracy</i>	-.746*	-.671*	.044	.151	-.400	-.476
	<i>Poor glucoregulators</i>	<i>Hits</i>	-.396	-.654	-.109	-.085	-.168	-.648
		<i>Accuracy</i>	-.397	-.647	-.075	-.051	-.274	-.698
	<i>Overall</i>	<i>Hits</i>	-0.465	-.593*	-0.041	0.011	-0.194	-.544*
		<i>Accuracy</i>	-.519*	-.614*	0.001	0.057	-0.292	-.597*

\* indicates  $p < .05$

**Table 3.** Correlations between behavioural performance, and P2 mean amplitude and peak latency to targets and non-targets in good and poor gluco regulators.

			Fz		Cz	
			target	non-target	target	non-target
<i>P2 Amplitude</i>	<i>Good gluco regulators</i>	<i>Hits</i>	-.406	-.374	-.257	-.305
		<i>Accuracy</i>	-.280	-.402	-.240	-.360
	<i>Poor gluco regulators</i>	<i>Hits</i>	-.292	-.173	-.368	-.108
		<i>Accuracy</i>	-.233	-.158	-.342	-.114
	<i>Overall</i>	<i>Hits</i>	-0.425	-0.351	-0.433	-0.273
		<i>Accuracy</i>	-0.414	-0.391	-0.45	-0.323
<i>P2 Latency</i>	<i>Good gluco regulators</i>	<i>Hits</i>	-.494	-.565	-.177	-.271
		<i>Accuracy</i>	-.418	-.603	-.258	-.444
	<i>Poor gluco regulators</i>	<i>Hits</i>	-.679	-.492	-.737*	-.533
		<i>Accuracy</i>	-.705	-.522	-.796*	-.580
	<i>Overall</i>	<i>Hits</i>	-.641**	-.536*	-.634**	-.539*
		<i>Accuracy</i>	-.675**	-.598*	-.686**	-.605*

\* indicates  $p < .05$

\*\* indicates  $p < .01$

**Table 4.** Correlations between behavioural performance, and P3 mean amplitude and peak latency to targets and non-targets in good and poor glucoregulators.

			CPI		Cz		CP2		Pz	
			target	non-target	target	non-target	target	non-target	target	non-target
<i>P3 Amplitude</i>	<i>Good glucoregulators</i>	<i>Hits</i>	.535	-.147	.627	-.129	.627	-.112	.556	.029
		<i>Accuracy</i>	.527	.023	.545	-.014	.656	.043	.625	.221
	<i>Poor glucoregulators</i>	<i>Hits</i>	.593	.623	.590	.731*	.533	.591	.469	.488
		<i>Accuracy</i>	.581	.578	.582	.685	.514	.554	.454	.469
	<i>Overall</i>	<i>Hits</i>	0.463	0.385	0.453	0.367	0.376	0.273	0.341	0.319
		<i>Accuracy</i>	0.437	0.349	0.422	0.318	0.346	0.242	0.322	0.309
<i>P3 Latency</i>	<i>Good glucoregulators</i>	<i>Hits</i>	-.544	-.662	-.653	-.557	-.474	-.715*	-.661	-.910**
		<i>Accuracy</i>	-.567	-.708*	-.753*	-.597	-.562	-.741*	-.671*	-.909**



<i>Poor</i>									
	<i>Hits</i>	-0.595	-0.736*	0.096	-0.629	-0.454	-0.434	-0.406	-0.383
<i>glucoregulators</i>									
	<i>Accuracy</i>	-0.607	-0.784*	0.080	-0.670	-0.476	-0.493	-0.473	-0.473
<i>Overall</i>									
	<i>Hits</i>	-0.394	-0.579*	-0.16	-0.46	-0.382	-0.356	-0.273	-0.371
	<i>Accuracy</i>	-0.441	-0.641*	-0.25	-0.510*	-0.449	-0.424	-0.345	-0.464

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\* indicates  $p < .05$

\*\* indicates  $p < .01$

**Figure 1.** OGTT data for good and poor gluco regulators (0 represents baseline fasting levels; standard errors shown in error bars).

**Figure 2.** The grand average ERPs at electrode sites P7, P8, PO3, PO4, O1 and O2. ERPs for the infrequent targets and frequent non-targets of both good and poor gluco regulators are displayed for the P1 component (130 – 165 ms, light blue shading).

**Figure 3.** The grand average ERPs at electrode sites P7, Pz, and P8. ERPs for the infrequent targets and frequent non-targets of both good and poor gluco regulators are displayed for the N170 component (170 – 235 ms, green shading).

**Figure 4.** The grand average ERPs at electrode sites Fz and Cz. ERPs for the infrequent targets and frequent non-targets of both good and poor gluco regulators are displayed for the P2 component (180 – 265 ms, dark blue shading).

**Figure 5.** The grand average ERPs at electrode sites Cz, CP1, CP2 and Pz. ERPs for the infrequent targets and frequent non-targets of both good and poor gluco regulators are displayed for the P3 component (545 – 780 ms, purple shading).