Neural, Hormonal, and Cognitive Correlates of Metabolic Dysfunction and Emotional Reactivity

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ABSTRACT

Objective: Prediabetes and type 2 diabetes (i.e., hyperglycemia) are characterized by insulin resistance. These problems with energy metabolism may exacerbate emotional reactivity to negatively valenced stimuli and related phenomena such as predisposition toward negative affect, as well as cognitive deficits. Higher emotional reactivity is seen with hyperglycemia and insulin resistance. However, it is largely unknown how metabolic dysfunction correlates with related neural, hormonal, and cognitive outcomes.

Methods: Among 331 adults from the Midlife in the United States study, eye-blink response (EBR) we cross sectionally examined to gauge reactivity to negative, positive, or neutrally valenced pictures from international affect picture system stimuli proximal to an acoustic startle probe. Increased EBR to negative stimuli was considered an index of stress reactivity. Frontal alpha asymmetry, a biomarker of negative affect predisposition, was determined using resting electroencephalography. Baseline urinary cortisol output was collected. Cognitive performance was gauged using the Brief Test of Adult Cognition by telephone. Fasting glucose and insulin characterized hyperglycemia or the homeostatic model assessment of insulin resistance.

Results: Higher homeostatic model assessment of insulin resistance corresponded to an increased startle response, measured by EBR magnitude, for negative versus positive stimuli ($R^2 = 0.218$, $F(1,457) = 5.48$, $p = .020$, euglycemia: M(SD) = .092(.776), hyperglycemia: M(SD) = .120(.881)). Participants with hyperglycemia versus euglycemia showed greater right frontal alpha asymmetry ($F(1,307) = 6.62$, $p = .011$, euglycemia: M(SD) = .018(.167), hyperglycemia: M(SD) = −.029(.160)), and worse Brief Test of Adult Cognition by telephone arithmetic performance ($F(1,284) = 4.25$, $p = .040$, euglycemia: M(SD) = 2.390(1.526), hyperglycemia: M(SD) = 1.920(1.462)). Baseline urinary cortisol (log10 μg/12 hours) was also dysregulated in individuals with hyperglycemia ($F(1,324) = 5.09$, $p = .025$, euglycemia: M(SD) = 1.052 ± .332, hyperglycemia: M(SD) = .961(.362)).

Conclusions: These results suggest that dysmetabolism is associated with increased emotional reactivity, predisposition toward negative affect, and specific cognitive deficits.

Key words: cortisol, EEG, HOMA-IR, insulin resistance, International Affective Picture System, type 2 diabetes.

INTRODUCTION

One third of Americans are obese (1); 22 million adults have type 2 diabetes and nearly 40% of middle-aged adults develop pretype 2 diabetes (2). Pretype 2 diabetes etiology is characterized by insulin resistance (IR), which is a reduced cellular response to insulin (3). Although it is well established that IR and type 2 diabetes contribute to cardiovascular disease and other pathologies, they also affect behavior. For example, IR is related to deficits in cognitive (4) and affective processing, particularly reactivity to psychological stress in humans (5) and monkeys (6). IR in euglycemic or hyperglycemic (i.e., pretype 2 diabetes and type 2 diabetes) participants is also associated with neural sequelae that affect these behavioral outcomes (6–8). It is unclear how IR affects cognitive and emotional processing. It has been suggested that oxidative stress, neuronal apoptosis, neuroinflammation, and electrophysiological abnormalities can cause architectural changes and contribute to brain dysfunction in type 2 diabetes (9).

IR and hyperglycemia also manifest with major depressive disorder (MDD) and several other anxiety and mood disorders. Participants with MDD showed impaired insulin sensitivity (i.e., IR) after an oral-glucose tolerance test that was resolved after antidepressant treatment (10). Indeed, if depression is resolved, fasting glucose levels tend to improve (11,12). Recent meta-analyses suggest that MDD (13) and bipolar disorder (14) are associated with higher rates of type 2 diabetes. For example, individuals with type 2 diabetes are twice as likely to have MDD (15) and impaired cognitive performance (16,17) compared with those without type 2 diabetes. Conversely, MDD may increase the risk of developing type 2

EBR = eye-blink response, **EEG** = electroencephalography, **EMG** = electromyography, **HOMA-IR (log10)** = homeostatic model assessment of insulin resistance (logarithm base 10), **IAPS** = International Affective Picture System, **IR** = insulin resistance, **MDD** = major depressive disorder, **WHR** = waist-hip ratio

SDC Supplemental Content

From the Department of Food Science and Human Nutrition (Wolf, Willette), Iowa State University, Ames; Institute on Aging (Tsenkova, Ryff, Davidson), and Department of Psychology (Ryff, Davidson), University of Wisconsin-Madison; Center for Healthy Minds (Davidson), and Waisman Laboratory for Brain Imaging and Behavior (Davidson), University of Wisconsin-Madison; Departments of Psychology (Willette) and Biomedical Sciences (Willette), Iowa State University, Ames; and Department of Neurology (Willette), University of Iowa, Iowa City.

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diabetes (18). Some of this increased risk of MDD, and in general emotional reactivity, may be due to stigma and discrimination toward individuals who are obese (19). However, IR may be a critical biological mechanism underlying emotional reactivity and psychopathology (8,20,21). It is chronic stress rather than acute stress that has an influence on human physiology (22,23). Animals studies show chronic stress leads to low-grade chronic inflammation in the brain (24), resulting in macrophage infiltration in the gut that can induce metabolic dysfunction (25).

Thus, it is important to further investigate biological, psychological, and neural correlates examining associations between behavioral reactivity and metabolic dysfunction. The International Affective Picture System (IAPS) is commonly used for experimental investigation of emotion and attention. Brain regions have been examined with regard to which areas are associated with emotional reactivity. Multiple studies have shown the visual cortex being activated when viewing emotional pictures (26,27). The visual cortex has differing activation between the left and right hemisphere in response to emotional stimuli (28,29). Other brain regions showing activation include the amygdala-hippocampal region (26), dorsolateral prefrontal cortex (30), basal ganglia (26), ventromedial prefrontal (vPFC) and medial orbitofrontal cortex (26), and anterior cingulate (26,30). Human (20,21,31,32) and monkey (7) studies have demonstrated that IR is related to brain atrophy, as well as less glucose uptake in humans (33), in most of these areas but particularly vPFC (21). The vPFC is essential for top-down modulation of stress-induced emotional reactivity, as well as medial temporal areas such as amygdala and hippocampus that in part grade for threat detection and emotional regulation (34).

One method of examining emotional reactivity is the eye-blink startle response, which is an involuntary periorbital eye reflex to a typically loud acoustic stimulus. Vrana and colleagues (35) initially found that pairing a startle probe with an aversive or pleasant stimulus respectively facilitated or inhibited the automatic eye-blink response, allowing assessment of state and trait affective disposition as well as emotional reactivity (36,37). The IAPS have been commonly used as a primary or foreground stimulus paired with acoustic startle (38). It is also the case that emotion-modulated startle varies based on when IAPS stimuli are presented. For example, Larson and colleagues (39) found that startle modulation of the eye-blink response disappears 4 to 7 seconds after a given picture disappears from the screen, suggesting that examining early versus late eye-blink startle response may help better distinguish affect facilitation or inhibition versus a response just due to the startle probe.

Despite associations between stress reactivity and metabolic dysfunction, a full understanding of how this relates to the startle eye-blink response and other neural correlates remains unknown. Therefore, it was worthwhile to determine in otherwise healthy, middle-aged adults if hyperglycemia and IR were related to psychophysiological and behavioral measures of psychological emotional reactivity or negative affect predisposition. Our central hypothesis is that metabolic dysfunction is related to neural biomarkers of emotional reactivity. By using electromyography (EMG) and electroencephalogram (EEG) data from the MIDUS (Midlife in the United States) study (40), differences between healthy adults and those with IR and pretype 2 diabetes or type 2 diabetes (i.e., hyperglycemia) can be identified. In this study, we investigated whether hyperglycemia and IR were associated with: (1) worse cognitive performance and dysregulated cortisol and (2) higher psychophysiological measures of emotional reactivity, both at rest and during picture presentation paired with acoustic startle using eye-blink response (EBR).

RESEARCH DESIGN AND METHODS

Participants

The data for this study were obtained from the MIDUS database (http://www.midus.wisc.edu/midus2). MIDUS II is a cross-sectional study that started in 2002, which was a follow-up to the original MIDUS I study launched in 1995. The follow-up study was completed by 2009 and included a collection of neuroscience data in a subset of 331 respondents from 1255 MIDUS participants who were part of the biomarker project within the study. The MIDUS protocols were reviewed by the University of Wisconsin-Madison Institutional Review Board. All participants signed verbal consent for the biomarker project and gave verbal consent for the telephone and mail survey data before the initiation of the study. Participants were excluded from the analysis if biomarker data were missing or if 2 of 3 EBR measurements were missing. Among the participants with biomarker data, there were no significant differences between age, sex, income level, and marital status (41). However, Love et al. (41) indicated that compared with the larger MIDUS sample from which they were drawn, the biomarker participants had significantly higher educational levels, with 52.2% attending high school/some college and 42.1% being a college graduate or beyond. The sample also was predominately white (78.3%), and 13.8% of responders reported that they smoke cigarettes (41).

Biological Measures

As described in the MIDUS protocol (42), fasting blood samples were collected during an overnight stay. Cobas Integra Systems assay (Roche Diagnostics, Indianapolis, IN) was used to measure glycated hemoglobin (HbA1c) with an interassay Coefficients of Variability (CV) of the control 1.1% to 3.4%, an intra-assay CV of 0.43%, and a reference range of 4.0% to 5.6%. An enzymatic assay photometrically measured fasting glucose (Roche Modular Analytics P, Indianapolis, IN) and an ADVIA Centaur Insulin immunoassay (Siemens, Malvern, PA) was used to measure fasting insulin. Insulin interassay CV of the control was 2.4% to 4.6%, an intra-assay CV of 2.5% to 4.0%, and a reference range of 4 to 27 uIU/mL. Glucose interassay CV of the control was 1%, an intra-assay CV of 1%, and a reference range of 70 to 99 mg/dL. An established formula was used to calculate homeostatic model assessment of IR (HOMA-IR) (43), which is used to measure peripheral IR. Urine was collected for 12 hours to measure neuroendocrine hormones such as cortisol and creatinine, which were isolated using high-performance liquid chromatography - mass spectrometry.

Determination of Hyperglycemia (Pretype 2 Diabetes, Type 2 Diabetes)

Current criteria from the American Diabetes Association were used to define presence of prediabetes (HbA1c between 5.7% and 6.5% or glucose between 100 and 126 mg/dL, and not taking diabetes medications) and diabetes (HbA1c > 6.5%, fasting glucose > 126 mg/dL, or taking medications that lower glucose levels such as Metformin) (44).

Affective Neuroscience Assessments

The neuroscience project of MIDUS II investigated emotional reactivity and recovery by obtaining EMG data and EBR magnitude and amplitude in response to 90 IAPS pictures of 30 positive, 30 neutral, or 30 negative emotional valence using EMG (27). Please see Figure S1 (Supplemental Digital Content, http://links.lww.com/PSYMED/A464) for an illustration of stimulus presentation. Facial muscle recordings such as EBR provide differential facets of emotional response stemming from processing

emotional stimuli (45,46). EBR provides objective estimates of time, magnitude, and amplitude of emotional response during and after IAPS.

For the EBR scoring, EBR magnitudes were calculated by subtracting the amount of integrated EMG at reflex onset from that at peak amplitude (maximum amount of integrated EMG between 20 and 120 milliseconds after probe onset). Trials with no detected EBR were assigned a magnitude of zero and included in the analysis. EBR magnitudes were log-transformed to normalize the data, then *z*-scored to range-correct the data separately for each participant. A participant's data were excluded when the participant did not respond with a detectable EBR on less than 75% of the total number of probes. EBR amplitudes were calculated similarly, except trials with no detectable eye-blink reflex were excluded from the analysis (47). Text S1 (Supplemental Digital Content, http://links.lww.com/PSYMED/A464) describes additional EBR processing.

After accounting for missing EBR and HOMA-IR data, our analysis included approximately 123 euglycemia, 89 pretype 2 diabetes, and 44 type 2 diabetes individuals. EBR is an objective index of the startle response. The human startle response is commonly used in research studies and in clinical practice to measure central nervous system activity and EMG is frequently used to obtain it.

EBR in response to acoustic startle stimuli was measured by placing two mini electrodes below the eye. The pictures shown to the participants were from the IAPS (27). For a given trial, the acoustic startle stimuli (105 dB) was administered for 50 milliseconds during one of the following three phases: (1) the "early" phase at 2900 milliseconds after picture onset while the picture was on the screen to assess reactivity; (2) the "middle" phase at 400 milliseconds after picture onset; and (3) the "late" phase at 1900 milliseconds after picture offset and removal to assess longer-term recovery (Figure S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A464). Schaefer et al. (48,49) showed across all valences that EBR at a second "middle" phase probe occurring 400 milliseconds after picture offset had decreased magnitude, which suggested that prepulse inhibition may have affected the second probe magnitude because close temporal proximity to the picture offset. Taking their finding into consideration, we dropped this time point from our analysis.

Electroencephalography

EEG data were also collected to assess scalp electrical activity and thereby indirectly assess cortical brain activity. A geodesic electrode net on the scalp with 128 channels of EEG was used to collect the data (http://www.egi.com). Resting frontal asymmetry was defined as the difference between the right and left side prefrontal cortex activation, as measured by EEG. Higher activation of the left side of the prefrontal cortex compared with the right is related to a predisposition toward positive affect (50), whereas higher activation of the right side of the prefrontal cortex compared with the left is associated with predisposition toward negative affect (46). This is gauged using Alpha wave frequency. Resting EEG asymmetry was collected before image presentation. To constrain type 1 error, we focused on alpha wave output comparing the f3/f4 and f7/f8 channels, which have been used to assess right frontal asymmetry (50). EEG methodology is further described in Text S2 and the EEG lower and upper alpha bands are shown in Table S1 (Supplemental Digital Content, http://links.lww.com/PSYMED/A464).

Cognitive Assessment

Part of the Brief Test of Adult Cognition by telephone included a number completion series and a category fluency task. Accuracy and total number correct of 1 to 5 numbers series tasks were recorded and the number of unique words mentioned in a particular category in 15 seconds. Number series tests have been used to measure fluid intelligence and reasoning (51).

Statistics

All analyses were conducted using SPSS 23 (IBM Corp, New York, NY). Fasting labs, including glucose, insulin, and HOMA-IR, were log-transformed to produce a normal distribution. Restricted maximum likelihood linear mixed models were used to analyze the main effects or interactions of HOMA-IR or hyperglycemia on EBR during the early versus late phase of IAPS stimulus presentation for the following contrasts: (1) negative minus positive and (2) negative minus neutral. Covariates include age, sex, and waist-hip ratio (52–54). The same model was used to predict resting frontal EEG asymmetry, as well as cognition and cortisol output during the arithmetic task. One subject had predictor values greater than 3 standard deviations from the mean and was excluded from analysis. Significance was determined as $p < .05$.

RESULTS

Data Summary

Table 1 lists demographics, HOMA-IR, EEG, EBR, and other baseline sample characteristics, as well as comparisons between the euglycemia versus hyperglycemia groups.

EMG EBR Startle Reflex

For EBR startle reflex magnitude, there was a HOMA-IR by trial phase interaction ($F(1,457) = 5.48$, $p = .020$), indicating that HOMA-IR differentially predicted EBR for various trial phases. Specifically, higher HOMA-IR corresponded to an increased startle response for negative relative to positive stimuli ($R^2 = .218$, $p < .001$) (Fig. 1A), but not during the late phase after the image disappeared (Fig. 1B). For EBR startle reflex amplitude, participants with pretype 2 diabetes and type 2 diabetes were more responsive for negative relative to neutral stimuli during early picture onset than euglycemic participants ($F(1, 290) = 4.06$, $p = .045$).

EEG Frontal Asymmetry

For resting EEG, subjects with pretype 2 diabetes or type 2 diabetes had lower alpha wave output in right versus left frontal areas including f3/f4 ($F(1,307) = 6.62$, $p = .011$) (Fig. 2) and f7/f8 ($F(1,307) = 5.99$, $p = .015$) (euglycemia mean ± SEM: .0007 ± .0064; hyperglycemia mean ± SEM: −0.0210 ± .0062), which reflects greater right frontal activity. Higher log HOMA-IR was not related to f3/f4 output ($p = .310$) but was modestly associated with greater f7/f8 right frontal asymmetry ($R^2 = .030$, $p = .002$).

Basal Cortisol

At baseline, a main effect for cortisol urine output showed that baseline urinary cortisol was lower in type 2 diabetes and pretype 2 diabetes participants compared with those with normal blood glucose levels ($F(1,324) = 5.09$, $p = .025$) (Fig. 3). Similarly, higher HOMA-IR was related to lower baseline urine cortisol corrected for creatinine ($F(1,324) = 9.27$ $p = .003$).

Cognitive Assessment

Participants with pretype 2 diabetes or type 2 diabetes showed lower total performance scores on the arithmetic task than those with euglycemia ($F(1,284) = 4.25$, $p = .040$) (Fig. 4). Lower repetition scores on the Brief Test of Adult Cognition by telephone category fluency task was not related to glycemic status ($F(1,286) = 1.27$, $p = .282$).

DISCUSSION

Our results suggest that some degree of metabolic dysfunction is related to brain-based emotional reactivity, urinary cortisol levels, and cognitive function. Individuals with pretype 2 diabetes and

TABLE 1. Demographics and Summary Indices

	Euglycemic (n = 150)	Pretype 2 Diabetes (n = 109)	Type 2 Diabetes (n = 65)	All Participants (N = 324)
Age, y	50.55 ± 0.87	53.33 ± 1.05	58.35 ± 1.45	53.05 ± 0.63
Sex (F/M), n	89/61	54/55	38/27	181/143
Currently smoking cigarettes, n	21	16	12	49
On glucose lowering medication, n	0^a	0^a	40^b	40
BMI, kg/m^2	28.82 ± 0.54	31.08 ± 0.60	33.13 ± 0.88	30.45 ± 0.38
WHR	0.88^a ± 0.01	0.91^a ± 0.01	0.94^b ± 0.01	0.90 ± 0.01
HOMA-IR (log10)	0.30 ± 0.03^a	0.52 ± 0.03^b	0.74 ± 0.05^c	0.44 ± 0.02
Urine cortisol (log10 µg/12 h)	1.06 ± 0.03	0.97 ± 0.03	0.93 ± 0.05	1.00 ± 0.02
EEG f3/f4 alpha, µV^2	0.02 ± 0.01	−0.04 ± 0.02	−0.01 ± 0.02	−0.01 ± 0.01
HbA1c%	5.61 ± 0.02^a	6.00 ± 0.04^a	7.81 ± 0.24^b	6.17 ± 0.07
EBR Mag (avg negative z-score)	0.01 ± 0.03	0.07 ± 0.04	0.07 ± 0.05	0.04 ± 0.02
EBR Mag (avg neutral z-score)	−0.01 ± 0.03	−0.05 ± 0.04	−0.01 ± 0.05	−0.03 ± 0.02
EBR Mag (avg positive z-score)	−0.04 ± 0.03	−0.06 ± 0.03	−0.01 ± 0.04	−0.04 ± 0.02
EBR Amp (avg negative z-score)	0.04 ± 0.02	0.02 ± 0.02	0.03 ± 0.03	0.03 ± 0.01
EBR Amp (avg neutral z-score)	0.04 ± 0.02	0.04 ± 0.02	0.02 ± 0.03	0.03 ± 0.01
EBR Amp (avg positive z-score)	-0.06^a ± 0.02	−0.04 ± 0.02	-0.03^b ± 0.03	−0.05 ± 0.01

F, female; M, male; BMI, body mass index; WHR, waist-hip ratio; HOMA-IR (log10) = homeostatic model assessment of insulin resistance (logarithm base 10); EEG = electroencephalography; HbA1c, glycated hemoglobin; EBR = eye-blink response; Mag = magnitude; Amp = amplitude.

Variables are shown as mean ± standard error of the mean or frequency count. Superscript letters per row indicate a significant difference of one subgroup versus another subgroup with a different superscript letter, based on a multivariate analysis of variance with a Sidak post-hoc testing. For example, the type 2 diabetes, prediabetes, and euglycemic groups each have a significantly different mean value versus the other groups. For EBR magnitude (avg positive), euglycemic and type 2 diabetes groups differ, whereas the prediabetes group shows no difference versus either of those groups.

type 2 diabetes showed a heightened startle-related stress response to negative versus positive stimuli during picture presentation, but not after picture offset during the recovery period. These results suggest that IR predicts heighted early stress response for "unpleasant" versus "pleasant" emotional stimuli. It has been previously shown that IR is related to deficits in cognitive and affective processing among rhesus monkeys (7) and humans (5). The link between stress and insulin is not clear and requires further investigation. Long-term calorie restriction substantially reduces IR and stress reactivity in rhesus monkeys, who do not manifest bias toward obese cage mates, suggesting that the association is at least partly neurobiological in origin (6,7). It is interesting to

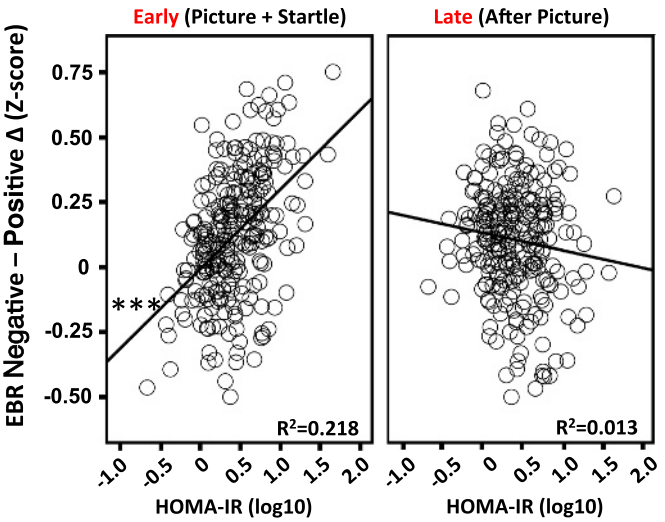

FIGURE 1. EBR magnitude changes across Time EBR as predicted by HOMA-IR. The mean EBR magnitude reflects the difference between "pleasant" and "unpleasant" images during either the early or late phases of picture presentation. EBR reflex magnitude in microvolt was measured during either the early phase (i.e., 2900 milliseconds after picture appears) or late phase (i.e., 1900 milliseconds after picture disappears). EBR signal was log-transformed to normalize data, then z-scored per subject to control for the large individual differences that often occur with EMG. ***$p < .001$. Covariates included age, sex, HOMA-IR, WHR, and diabetes status. HOMA-IR (log10), homeostatic model assessment of insulin resistance log-transformed; EBR, eye-blink response. Color image is available only in online version (www.psychosomaticmedicine.org).

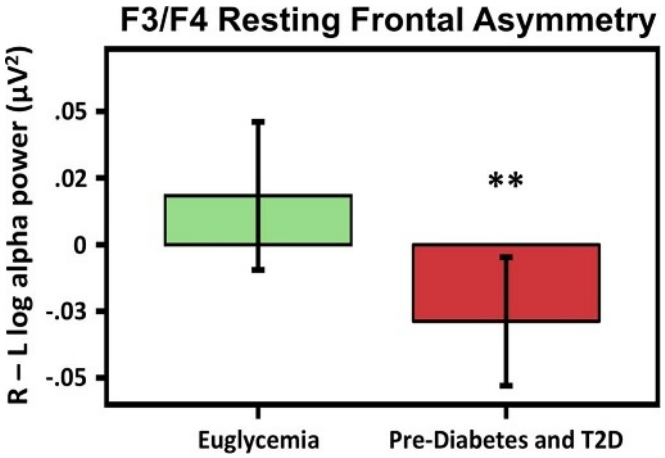

FIGURE 2. f3/f4 resting frontal asymmetry differences in R vs. L frontal EEG alpha power magnitude among individuals with euglycemia or hyperglycemia. Data are presented as M (SD). Covariates included age, sex, and WHR. EEG, electroencephalography; L, left; R, right; F, frontal; SD, standard deviation; T2D, type 2 diabetes; WHR, waist-hip ratio. Color image is available only in online version (www.psychosomaticmedicine.org).

note that calorie restriction in aged rhesus monkeys reduces IR, emotional reactivity to novel stressors, and related neurodegeneration in the vPFC and hippocampus without affecting activity or attention behavior (6,7). This suggests that weight loss and lower IR may reduce emotional reactivity. It should be noted that waist-hip ratio (WHR) was covaried in this report's statistical models, though, suggesting that variance related to weight or adiposity may not be directly affecting associations with IR and glycemic status.

Alternatively, the start of IR could contribute to further weight gain. Pathologies of excess stress may affect eating behaviors and thus induce obesity (55,56). Most studies have reported that during times of stress, individuals change their eating behaviors to consume more calories rather than less calories (57–59). Indeed, individuals who are overweight are more likely to gain weight in response to stress than those who are of a normal weight (59). Stress can induce corticosteroids, which can increase one's appetite for food (60), but stress can also lead to a decrease in food intake (61). Increased insulin levels can be induced by stress, which in turn has been shown to decrease food intake (62). Insulin and leptin receptors in the arcuate nucleus of the hypothalamus help sustain energy by governing food intake (63). Other examples of signaling molecules involved are cholecystokinin (64) and tumor necrosis factors (65), as well as lipids (66) and sugars that can affect the hypothalamus but also limbic and autonomic brain regions (67). Some individuals may be predisposed to IR because of epigenetics and genetics. For instance, the fat mass and obesity-related gene (FTO) has been associated with obesity, with an approximately 0.4 kg/m^2 of rise in BMI correlated with each copy of a specific allele (68).

Our study also observed modestly dysregulated cortisol output due to hyperglycemia, suggesting dysregulation of the hypothalamic-pituitary-adrenal axis underlying stress perception and response (69). Abraham et al. (70) similarly found weak to

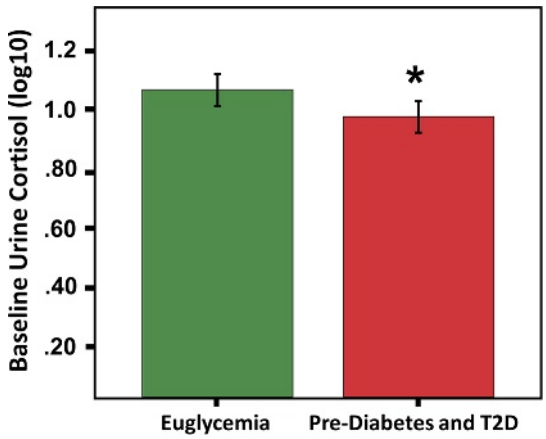

FIGURE 3. Baseline urine cortisol differences in baseline urine cortisol (log10 μg/12 h) adjusted for creatinine among participants with euglycemia or hyperglycemia. Data are presented as M (SD). Covariates included age, sex and diabetes status. μg, microgram; g, gram; T2D, type 2 diabetes; log10, logarithm base 10; SD, standard deviation. Color image is available only in online version (www.psychosomaticmedicine.org).

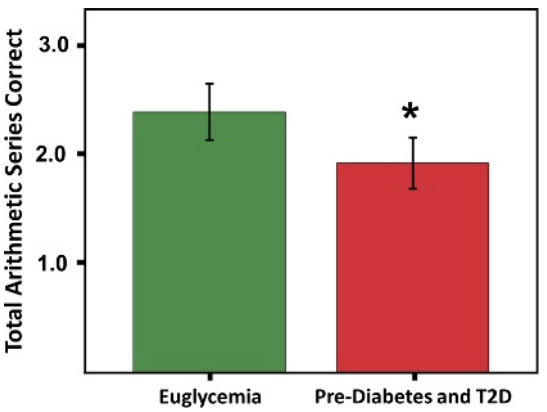

FIGURE 4. Total arithmetic series correct differences in total arithmetic series answers correct among participants with euglycemia and or hyperglycemia. Data are presented as M (SD). Covariates included age, sex, and diabetes status. T2D, type 2 diabetes; SD, standard deviation. Color image is available only in online version (www.psychosomaticmedicine.org).

moderate associations between metabolic dysfunction markers, cortisol, and self-reported stress. Another study showed that individuals with type 2 diabetes had flattened cortisol during the day compared with others in the study who did not have type 2 diabetes (71). The authors suggested that individuals with type 2 diabetes showed heightened cortisol levels in the evening when they would normally decline (71). Regardless, hyperglycemia has been related to increased anxiety and depression scores using measures such as the Patient Health Questionnaire (PHQ-9) (72) and the Generalized Anxiety disorder scale (GAD-7) (72).

Resting EEG confirmed our EBR findings, where greater right frontal asymmetry was seen in pretype 2 diabetes and type 2 diabetes. This is a well-established neural biomarker associated with predisposition toward negative affect (46). Makine et al. (73) similarly found that individuals with type 2 diabetes who are not yet on insulin were more likely to be depressed and have negative attitudes about insulin therapy than nondiabetic controls. Our EEG results showed very modest associations with HOMA-IR compared with pretype 2 diabetes and type 2 diabetes, suggesting that overt metabolic disease such as type 2 diabetes, but not relatively mild dysfunction such as IR, may be related to a neurobiological predisposition to focus on negative affect (46). More research is needed at the behavioral and biological levels that link psychological stress to type 2 diabetes related morbidity.

Our study found that individuals with type 2 diabetes and pretype 2 diabetes scored worse on a math task than euglycemic individuals. There is strong evidence to suggest that type 2 diabetes is related to worse cognitive performance (17,74), possibly because of greater atrophy, white matter lesions, and infarcts in subcortical brain regions related to executive processes (75). It would be useful to see whether deficits in glucose metabolism or lower brain volume mediate these associations.

This study has several limitations and strengths. The participants of the MIDUS study live in a US geographical region that was predominantly white, so it may not be representative of the entire US population. In addition, the relationships were specific to glycemic status or IR, where hyperglycemia and hyperinsulinemia have overlapping but specific effects on neural function such as memory formation (31). Because this study is correlational in nature, it cannot be ruled that relationships we found are causal. Longitudinal data acquired in MIDUS or other cohorts may help establish more causal relationships. Specifically, data collected over time could help strengthen our understanding of whether variation in IR over time predicts subsequent changes in emotional reactivity, urinary cortisol, and cognitive performance or whether these correlates predict possible subsequent changes in IR. A strength of this research includes the large sample size, robust statistical methods (76) and the consistency of our findings with the existing literature. The relationship of HOMA-IR with the biological facets of emotional reactivity should prompt more research to uncover underlying mechanisms.

This study provides evidence that metabolic dysfunction may be related to the tendency to react more strongly to negative stimuli and, to increase frontal neural asymmetry, a biological measure that has been used to gauge predisposition of part of prefrontal cortex to attend to negative stimuli. This implies that metabolic dysfunction may be a potential mechanism that could partly modulate emotional reactivity to negative stimuli. Positive affect can lead to improved physical and mental health (77), and life-style interventions can prevent and delay type 2 diabetes for people at risk more than Metformin (78). IR mechanisms of action need to be further explored at a psychological, behavioral, and molecular level, to determine whether prevention and treatment methods can be used to improve cognitive function, emotional reactivity to negative stimuli, and more broadly affective predisposition.

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