Experimental Neurology 315 (2019) 15–20

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Research Paper

Childhood trauma and insulin resistance in patients suffering from depressive disorders

Carla Nasca[a,*], Kathleen Watson-Lin[b], Benedetta Bigio[a], Thalia K. Robakis[b], Alison Myoraku[b], Tonita E. Wroolie[b], Bruce S. McEwen[a,*], Natalie Rasgon[a,b,**]

[a] Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology, The Rockefeller University, New York, USA
[b] Center for Neuroscience in Women's Health, Stanford University, Palo Alto, CA 91304, USA

ARTICLE INFO

Keywords:
Insulin resistance
Insulin secretion
Childhood stress
Emotional abuse
Family history of type-2 diabetes
Risk factors

ABSTRACT

Objective: Insulin resistance (IR) is a metabolic dysfunction often co-morbid with major depressive disorder (MDD). The paths to development of MDD remain largely unspecified, highlighting a need for identification of risk factors. Here, we tested whether specific subscales of childhood trauma as well as family history of type-2 diabetes (Fam-Hx-Dm2) are risk factors for development of metabolic dysfunction and severity of depressive symptoms.

Research design and methods: We used a sample of 45 adults suffering from MDD that was well-characterized for insulin resistance and sensitivity as assessed by measures of fasting plasma glucose (FPG) plasma insulin (FPI) levels, body mass index (BMI), weight, homeostasis model assessment of insulin sensitivity (HOMA), Matsuda index as well as both glucose and insulin responses to oral glucose challenges. Severity of depressive symptoms was assessed with the Hamilton Depression Rating Scale (HDRS-21). Physical, sexual and emotional abuse as well as physical and emotional neglect were assessed with the Childhood Trauma Questionnaire. First- or second-degree relatives with type-2 diabetes defined fam-Hx-DM2.

Results: Individuals reporting higher rates of emotional abuse were more likely to have greater IR as showed by elevated FPI levels and HOMA. No association was found with any of the other subscales of childhood trauma (e.g., physical abuse). Similarly, Fam-Hx-DM2 was associated with greater degree of IR as shown by elevated FPI, HOMA, but also FPG, weight and BMI. Moreover, we report a relationship and interaction between Fam-Hx-DM2 and emotional abuse on severity of depressive symptoms. Specifically, emotional abuse and Fam-HX-DM2 predicted severity of depressive symptoms at HDRS-21. Also, severity of depressive symptoms was greater with higher reported rates of emotional abuse but only in patients with negative Fam-Hx-Dm2. Individuals reporting higher emotional abuse and negative Fam-Hx-Dm2 also showed higher FPG levels. Conversely, individuals reporting higher emotional abuse and positive Fam-Hx-Dm2 showed higher FPI levels. This data suggest that Fam-Hx-Dm2 may define two different metabolic endophenotypes.

Conclusions: Our findings suggest that Fam-HX-DM2 and emotional abuse represent separate risk factors for developing metabolic dysfunction (i.e.: IR) in patients suffering from MDD, and that the effects of emotional abuse on psychiatric illness may depend upon the personal characteristics, including Fam-Hx-DM2.

1. Introduction

Major depressive disorder (MDD) is a heterogeneous and complex disorder, increasingly considered as a *whole body* disease (Rasgon and McEwen, 2016; Nasca et al., 2019). Exposure to stress, including early life adversity (ELA), is a primary risk factor for development of MDD, and causes dysregulation of both peripheral and central systems (McEwen et al., 2015; Nemeroff, 2016; Nasca et al., 2018). Understanding the biological mechanisms underlying metabolic function in humans with MDD is a critical step to propose personalized medicine interventions for decreasing vulnerability to early life stress, and therefore, reducing risk for developing depressive disorders.

Metabolic dysfunction, including insulin resistance (IR) and obesity, is increasingly implicated in the pathophysiology of MDD as well as in

* Corresponding authors at: Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology, The Rockefeller University, New York, 1230 York Avenue, New York, NY 10065, USA.
** Corresponding author at: Center for Neuroscience in Women's Health, Stanford University, Palo Alto, CA 91304, USA.
E-mail addresses: cnasca@rockefeller.edu (C. Nasca), mcewen@rockefeller.edu (B.S. McEwen), nrasgon@stanford.edu (N. Rasgon).

https://doi.org/10.1016/j.expneurol.2019.01.005
Received 9 September 2018; Received in revised form 18 December 2018; Accepted 9 January 2019
Available online 11 January 2019
0014-4886/

its treatment (Watson et al., 2018; Rasgon et al., 2010a; Wroolie et al., 2015; Rasgon et al., 2010b; Lin et al., 2015; Rasgon and Jarvik, 2004; Austin et al., 2014; Kullmann et al., 2012; McIntyre et al., 2009). IR, a known precursor to the development of type-2 diabetes (DM2), is a reversible condition characterized by diminished ability of β-cells to respond to the action of insulin in stimulating glucose uptake in muscle and other tissues (Rasgon and McEwen, 2016; De Felice and Ferreira, 2014; Raison et al., 2006). Previous studies showed that IR is associated with disrupted memory and executive function, decreased hippocampal volumes as well as with aberrant intrinsic connectivity between the hippocampus and medial prefrontal cortex (Wroolie et al., 2015; Rasgon et al., 2011; Stemmle et al., 2009; Kenna et al., 2013). Recent reverse translational studies support these findings. Rodents with behavioral impairments and disrupted hippocampal and prefrontal cortex function showed IR. Interestingly, supplementation with the endogenous metabolite acetyl-L-carnitine (LAC) ameliorated both IR and the behavioral function, reinforcing the link between peripheral processes and behavioral modulation (Bigio et al., 2016; Fritz and McEwen, 1959; McEwen et al., 2016).

Recently, our group showed a deficiency of LAC, in two independent cohorts of patients suffering from MDD, and suggested a role for ELA in predicting a LAC deficiency (Nasca et al., 2018; Post, 2018). Specifically, an emotional subscale of childhood trauma (i.e.: emotional neglect) stood out as one of the most critical behavioral modifiers of the LAC deficiency (Nasca et al., 2018; Post, 2018). History of childhood trauma was also associated with more severe depressive symptoms (Nemeroff, 2016). Furthermore, our group suggested family history of type-2 diabetes (Fam-Hx-Dm2) as another risk factor for developing metabolic dysfunction (i.e.: IR) in women suffering from bipolar disorder (Rasgon et al., 2010a). Therefore, there is growing evidence suggesting a number of separate risk factors for development of metabolic dysfunction and mood disorders (Nemeroff, 2016; Williams et al., 2016; Danese et al., 2009; Post et al., n.d.). In this study, we aimed to create a unifying platform of risk factors contributing to metabolic and psychiatric domains.

Based upon this evidence, we tested whether specific subscales of childhood trauma as well as family history of type-2 diabetes (Fam-Hx-Dm2) contribute to the development of metabolic dysfunction and severity of depressive symptoms. To test this, we used a study sample that consisted of 45 adult subjects suffering from MDD that was well-characterized for indicators of IR.

2. Results

2.1. Roles of childhood trauma and family history of DM2 as separate risk factors for adulthood metabolic dysfunction

In our study sample that consisted of 45 adult subjects suffering from MDD that was well-characterized for indicators of IR, all 45 participants reported exposure to each type of trauma, namely physical, sexual and emotional abuse as well as physical and emotional neglect as assessed with the Childhood Trauma Questionnaire (CTQ). Furthermore, among the 45 subjects suffering from MDD, 42% reported positive Fam-Hx-DM2 as defined by first- or second-degree relatives with DM2, while the remaining 57% reported negative Fam-Hx-DM2. Demographic characteristics and severity of depressive symptoms at HDRS-21 did not differ between groups (Table 1).

We report that either Fam-Hx-DM2 or emotional abuse, but none of the other childhood trauma, were separately associated with IR in our study. Specifically, subjects who reported higher rates of emotional abuse had higher levels of FPI and HOMA (Fig. 1 A and B). Of note, no correlation was found between emotional abuse alone and severity of depressive symptoms ($F = 0.92$; Mean Square = 27.3; $p = 0.34$). We also report that Fam-Hx-DM2 was an independent risk factor for IR, in that subjects with positive Fam-Hx-DM2 had higher FPG, FPI, BMI and weight (Table 1). Further, subjects with positive Fam-Hx-DM2 had poorer insulin sensitivity as assessed with the homeostasis model assessment of insulin sensitivity (HOMA), the Matsuda index (Table 1) as well as with the oral glucose tolerance test (OGTT) as compared to patients with negative Fam-Hx-DM2 (Fig. 2A). No between-group differences were found in insulin responses to glucose challenges (Fig. 2B).

Table 1
Demographic, clinical and psychiatric characteristics in subjects with MDD dichotomized for negative and positive Fam-HX-DM2.

	Subjects with MDD_Mean(SD)	
	Negative Fam-HX-DM2 (n = 26)	Positive Fam-XH-DM2 (n = 19)
Age (years)	46.1 (2.8)	47.3 (3.3)
Height (cm)	167.4 (1.6)	164.4 (1.9)
Weight (Kg)	76.6 (15.8)	86.9(19.3)*
Education (years)	16 (0.5)	15.8 (0.5)
HDRS-21	14.7 (1.1)	14.0 (1.3)
BMI (Body Mass Index)	27.4 (1.2)	32.2 (1.5)*
Fasting Plasma Glucose (FPG, mg/dL)	93.5 (2.2)	100.5 (2.5)*
Fasting Plasma Insulin (FPI, mU/mL)	11.5 (1.1)	15.4 (1.3)*
HOMA	2.7 (0.3)	3.8 (0.3)**
Matsuda index	4.6 (0.4)	3.8 (0.3)*
Depressive episodes		
< 3	7 (26.9%)	5 (26.3%)
> 3	11 (42.3%)	10 (52.6%)
na	8 (30.8%)	4 (21.1%)

Demographic and psychiatric characteristics did not differ between groups. Patients suffering from MDD with positive Fam-Hx-DM2 showed worst IR with higher weight, BMI, FPG, FPI, HOMA and Matsuda index as compared to patients suffering from MDD and negative Fam-Hx-DM2.
Indicates significance between groups (*$p < 0.05$, **$p < 0.005$).

2.2. Interdependent role of childhood trauma and Fam-Hx-Dm2 on adulthood metabolic and behavioral psychiatric domains

We found an interaction between emotional abuse, but none of the other types of childhood trauma, and Fam-HX-DM2 in predicting severity of depressive symptoms at HDRS-21 (Table 2). Therefore, to study the relationship between emotional abuse and Fam-HX-DM2 on metabolic and behavioral psychiatric domains, we dichotomized our sample of 45 participants suffering from MDD into subjects with positive Fam-Hx-DM2 and subjects with negative Fam-HX-DM2. There was no between-group difference in the rates of each type of childhood trauma (Fig. 3).

Our data showed an association between emotional abuse and severity of depressive symptoms in subjects with negative Fam-HX-DM2, but not in subjects with positive Fam-HX-DM2 (Fig. 4A and B, A: $r = 0.4$, $p = 0.050$; B: $r = 0.14$, $p = 0.6$). Specifically, the higher rates of emotional abuse correlated with greater severity of depressive symptoms only in subjects with negative Fam-Hx-DM2 (Fig. 4A and B). This relationship remained significant upon multiple regression analysis controlling for age ($t = 0.2$, $p = 0.02$). Prediction models showed that emotional abuse predicted severity of depressive symptoms at HDRS-21 in subjects with negative Fam-HX-DM2 ($r = 0.4$, $p = 0.050$, $F = 4.3$).

Emotional abuse was also associated with FPG in subjects with negative Fam-HX-DM2, while again such an association was not observed in subjects with positive Fam-HX-DM2 (Fig. 4C and D). Specifically, the higher rates of emotional abuse correlated with higher levels of FPG only in subjects with negative Fam-Hx-DM2 (Fig. 4C and D, C: $r = 0.4$, $p < 0.04$; D: $r = 0.1$, $p = 0.6$). Prediction models showed that emotional abuse predicted FPG in subjects with negative FX-DM2 ($r = 0.4$, $p = 0.04$, $F = 4.6$). Instead, we found an association between emotional abuse and FPI in subjects with positive Fam-HX-DM2. The higher rates of emotional abuse correlated with higher FPI in subjects with

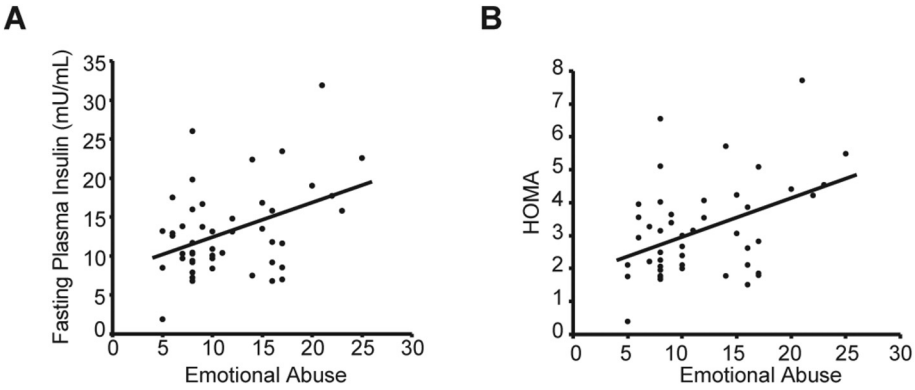

Fig. 1. Emotional abuse is associated with metabolic dysfunction. Higher levels of FPI (A) and HOMA (B) correlated with higher reported rates of emotional abuse in subjects with MDD (FPI: r = 0.6, p = 0.004; HOMA: r = 0.52, p = 0.004).

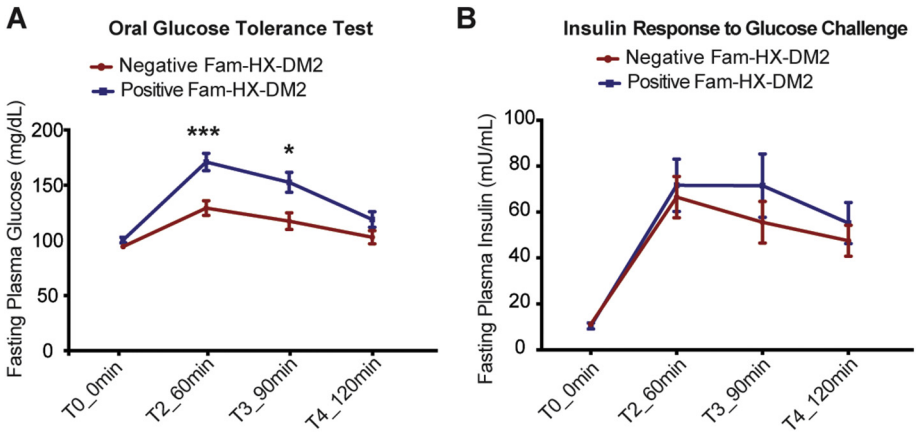

Fig. 2. Poorer insulin sensitivity after glucose challenges in patients suffering from MDD and positive Fam-Hx-DM2. (A) Between-group differences in glucose levels over time in response to glucose challenges with higher levels in patients suffering from MDD and positive Fam-Hx-DM2 as compared to patients negative Fam-Hx-DM2. (B) No between-group differences in insulin secretion after glucose challenges in patients suffering from MDD and positive Fam-Hx-DM2 as compared to those with negative Fam-Hx-DM2.

Table 2
Multiple regression analyses showing an interaction between emotional abuse, and none of the other types of childhood trauma, and Fam-HX-DM2 on severity of depressive symptoms.

	F	t	Mean square
Fam-HX-DM2 × Emotional abuse*	4.1	2.02	115.6
Fam-HX-DM2 × Physical abuse	0.0005	−0.02	0.01
Fam-HX-DM2 × Sexual abuse	0.1	0.37	4.3
Fam-HX-DM2 × Physical neglect	0.02	−0.14	0.6
Fam-HX-DM2 × Emotional neglect	1.1	1.05	33.4

* p = 0.04.

positive Fam-HX-DM2 (Fig. 4E and F, E: r = 0.2, p = 0.23; F: r = 0.6, p = 0.01).

3. Discussion

Our findings suggest early life adversity in the form of emotional abuse and family history of type-2 diabetes as separate risk factors for developing metabolic dysfunction (i.e.: IR) in patients suffering from MDD. Our findings also point to emotional abuse, and none of the other childhood maltreatments, as a risk factor for increased severity of depressive symptoms as a function of family history of type-2 diabetes.

Specifically, our data show that the consequences of emotional maltreatments in childhood differ from those of other types of childhood maltreatment such as physical and sexual abuse in agreement

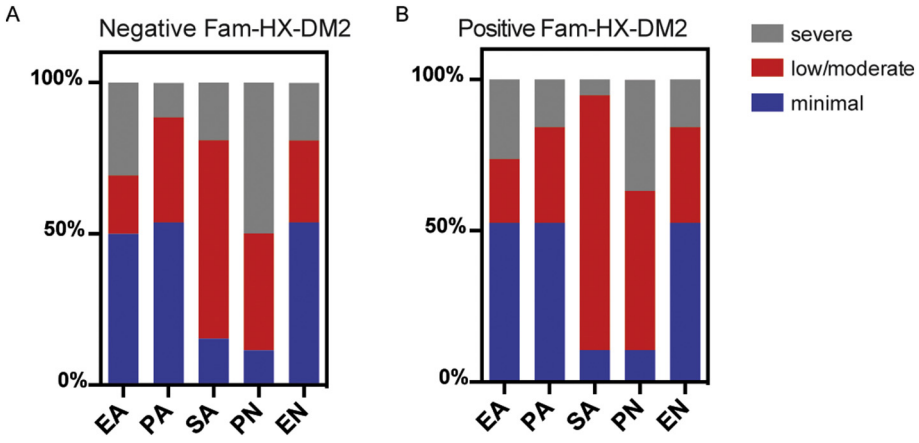

Fig. 3. Rates of each type of childhood trauma in subjects suffering from MDD dichotomized for negative and positive Fam-HX-DM2. Rates of emotional abuse (EA), physical abuse (PA), sexual abuse (SA), physical neglect (PN) and emotional neglect (EN) did not differ between patients suffering from MDD with negative Fam-Hx-DM2 (A) and positive Fam-Hx-DM2 (B).

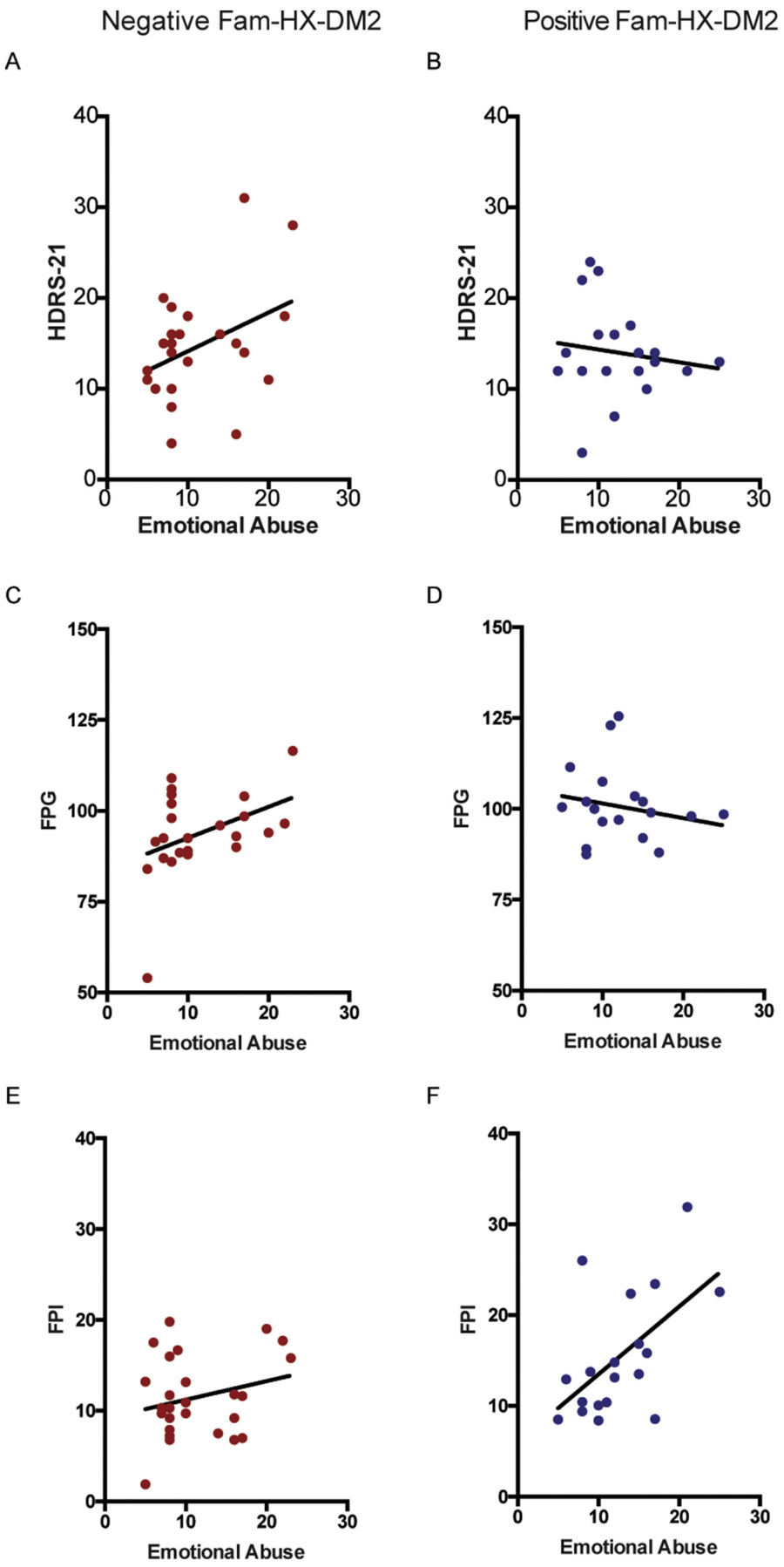

Fig. 4. Relationship between emotional abuse and Fam-HX-DM2 on severity of depressive symptoms (A–B), and metabolic function (C–D: fasting plasma glucose; E–F: fasting plasma insulin). (A–D) Patients with MDD and negative Fam-Hx-DM2, and not patients with MDD and positive Fam-Hx-DM2, exhibited i) greater severity of depressive symptoms and ii) higher FPG, with higher reported rates of emotional abuse (A: $r = 0.4$, $p = 0.050$; B: $r = 0.14$, $p = 0.6$; C: $r = 0.4$, $p \leq 0.04$; D: $r = 0.1$, $p = 0.6$). Conversely, FPI was higher with higher reported rates of emotional abuse in patients suffering from MDD and positive Fam-Hx-DM2, and not in patients with negative Fam-Hx-DM2 (E: $r = 0.6$, $p = 0.01$; F: $r = 0.2$, $p = 0.23$).

with previous reports (Nemeroff, 2016; Nasca et al., 2017a). The reported relationship between emotional abuse and IR is also consistent with previous reported associations between childhood adversities and obesity as well as other indicators of metabolic dysfunction in subjects suffering from mood disorders (Danese et al., 2009; Li et al., 2017).. Further supporting the reliability of our sample, our findings point to family history of DM2 as an independent risk factor for IR in agreement with a previously reported relationship between family history of DM2 and metabolic dysfunction in the general population (Fletcher et al., 2002). Although surprising, our reported interdependent relationship between emotional abuse and severity of depressive symptoms in subjects with negative, but not positive, family history of DM2 is akin of a previously documented negative association between family history of DM2 and psychiatric illness (Fan et al., 2013) (Tsuno et al., 2005). Furthermore, our findings showed that subjects with positive family history of DM2 are at a more advanced stage of IR than subjects with negative family history of DM2. Therefore, we reason that the extent of metabolic abnormalities in patients with positive family history of DM2 may preclude the relationship between childhood emotional abuse and severity of depressive symptoms. Another potential explanation can be a patient's vigilance to illness resulting from having a family member with DM2. This postulate is further supported by the theory of stress inoculation', i.e. the ability of stressful experience to foster adaptation to subsequent severe stress throughout the lifespan (Daskalakis et al., 2013; Lyons et al., 2009; McEwen and Wingfield, 2003; McEwen, 1998). Studies in rodents and non-human primates showed that i) brief periods of maternal separation blunted HPA axis responses to further stress events and ii) stress-inoculated non-human primates exhibited higher cognitive control and larger ventromedial prefrontal cortex volume (Lyons et al., 2009; Parker et al., 2006; Lyons et al., 2010; Lyons and Parker, 2007). Likewise, subjects who had worked in an uncomfortable environment in adolescence have a better perception of control upon further work-related stress (Mortimer and Staff J, 2004).

With regard to the observed relationship between emotional abuse, family history of DM2 and IR, future studies investigating the biological mechanisms underlying the role of IR in MDD may be relevant to better understand the differential patterns reported in this study. The relationships between emotional abuse and both severity of depressive symptoms and fasting glucose levels, but not fasting insulin, as a function of family history of DM2, suggests that family history of DM2 may define two different metabolic endophenotypes in subjects suffering from depression: one of compensatory hyperinsulinemia and another of hyperinsulinemia that may be independent of glucose metabolism. A potential biological underpinning of the suggested relationship between family history of DM2 and emotional abuse on IR may be that childhood emotional abuse causes a dysfunction in the pathway of acetyl-L-carnitine (LAC), an emerging biomarker of insulin resistance (Watson et al., 2018; Bigio et al., 2016; Nasca et al., 2017b). This possibility is supported by the recently reported relationship between a deficiency in LAC and a childhood emotional subscale in patients suffering from depressive disorders (Nasca et al., 2017a). Furthermore, the effects of insulin and glucose varies from tissue to tissue, and this complexity may be crucial to understand the effects of family history of DM2 in sustaining an appropriate insulin secretion capacity of β-cells with an impaired sensitivity to the action of insulin in patients suffering from MDD. Nonetheless our current findings suggest that some of relationships seen in this study could reflect not only a genetic liability, but also a type of epigenetic transmission. Future studies should explore whether a genetic liability and/or epigenetic mechanisms contribute to the reported effects.

Taken together, our findings suggest that early life adversity in the form of childhood trauma leads to lifespan effects on metabolic and psychiatric domains that depend upon the personal characteristics, among which family history of DM2. This knowledge may provide early windows of opportunities for personalized medicine interventions to decrease vulnerability to early life stress, and therefore, reduce risk for depressive disorders. Future research on a larger sample is warranted to further investigate the reported findings. Further studies, possibly with groups with MDD and not, are also needed to address some of the limitations inherent in our cross-sectional cohorts.

4. Methods

The Stanford University Institutional Review Board approved the current study in its entirety. After receiving detailed information regarding the study, participants provided informed consent prior to study enrollment. Study participants were recruited at the Department of Psychiatry & Behavioral Sciences at Stanford University.

4.1. Participants

The methodology for this study has been reported elsewhere (Wroolie et al., 2015; Lin et al., 2015). Briefly, inclusion criteria included being between 21 and 75 years old, having a body mass index (BMI) of 18.5 to 40 kg/m2, having at least 12 years of education, having a history of depression with at least 8 weeks of stable treatment as usual (TAU) for MDD. Exclusion criteria included a history of liver dysfunction, electroconvulsive therapy (ECT) within the previous 6 months, diagnosis of possible or probable any dementia or evidence of cognitive decline, history of Type I or Type II diabetes, history of significant CVD or myocardial infarction, cerebrovascular, pulmonary disease, or cancer, untreated hypothyroidism, unstable or untreated hypertension, known osteoporosis or prior history of non-traumatic fracture, history of a neurological disorder or evidence of neurologic or other physical illness that could produce cognitive deterioration. Current medication use was assessed at screening for all study participants. Participants were free of current substances of abuse as determined by a urine toxicology test at the time of screening. Participants were free of active infections and systemic illness as confirmed by medical history. Blood samples were obtained via antecubital venous collection using standard techniques and were drawn after a period of fasting (> 6 h). Information about subjects from this study have also been reported in previous papers (Lin et al., 2015). Family history of type-2 diabetes (Fam-Hx-DM2) was defined by first- or second-degree relatives having type-2 diabetes.

4.2. Clinical and psychiatric assessment

Clinical assessment consisted of a physical examination, including measures of height, weight, and BMI. Standard laboratory tests were performed to measure fasting plasma glucose (FPG), and fasting plasma insulin (FPI). Plasma markers of insulin sensitivity were assessed by using the 2-hour oral glucose tolerance test (OGGT) with blood draw at 30, 60, 90, and 120 min post loading with 75 g of oral glucose. Insulin sensititivy was determined at the same time points as for the OGGT and the Matsuda index was calculate as follows: Matsuda Index = 10,000/$(G_0 \times I_0 \times G_{mean} \times I_{mean})^{1/2}$ where G_0 is fasting glucose, I_0 is fasting insulin, G_{mean} is average serum glucose across entire OGGT period, and I_{mean} is mean insulin across entire OGGT period (Matsuda and DeFronzo, 1999). The homeostasis model assessment of insulin sensitivity HOMA was calculated as (fasting glucose * fasting insulin)/405. Symptoms of depression were assessed with the Hamilton rating scale for depression (HDRS-21). Trained clinicians conducted the Structured Clinical Interview for DSM-IV (SCID) to confirm MDD diagnosis and rule out exclusionary co-morbid conditions. All participants completed the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003) to assess for childhood traumatic experiences in five specific areas: physical, sexual and emotional abuse and physical and emotional neglect. The following standard cutoffs from the CTQ manual(Bernstein et al., 2003) were used to classify minimal, low/moderate and severe exposures to each trauma: < 6 for sexual abuse, < 8 for physical abuse and physical neglect, < 9 for emotional abuse, and < 10 for emotional

neglect (minimal); from 6 to 12 for sexual abuse, from 8 to 12 for physical abuse and physical neglect, from 9 to 15 for emotional abuse, and from 10 to 17 for emotional neglect (low/moderate); higher than 12 for sexual abuse, higher than 12 for physical abuse and physical neglect, higher than 15 for emotional abuse, and higher than 17 for emotional neglect (severe). Some information about subjects from the Icahn School of Medicine at Mount Sinai included in the current study was previously reported (Kiraly et al., 2017).

4.3. Statistical analysis

Statistical analyses were conducted using JMP Software from SAS (Statistical Analysis System, Institute, Cary, NC, USA). Predictive models were inferred using multiple regression analysis to assess the ability of the interaction between each CTQ area by family history of type-II diabetes to predict the dependent variable, HDRS-21. Two-tailed *t*-tests and chi-square analyses were used to compare, respectively, continuous and categorical demographic and clinical characteristics between the following two groups: subjects with MDD and FX-DM2 and subjects with MDD and no-FX-DM2. Multiple regression models were used to assess the relationship between each of the individual subscale of CTQ (independent variable) and the measures of both metabolic function and severity of depressive symptoms (dependent variables). Univariate and multivariate models were developed to test the unadjusted and adjusted associations for individual subscale of CTQ on each outcome. Analyses were controlled for factors including age, sex, and subscales of CTQ. Significance was set as two-sided of 0.05, and data are presented as mean ± SD, unless otherwise specified.

Authors' contribution

C.N., N.R. and B.S.M. wrote the manuscript. C.N., K.W., B.B., N.R. conceived statistical analyses, figures and tables. All authors contributed to interpret the data, discussed the results and conclusions, final version of the manuscript.

Acknowledgments

This work was supported by 1R21 MH093948-01A1 (SPO #50260) and ADA7-09-CT-50 (SPO #43365) to N.R., and by grants from the Robertson Therapeutic Development Foundation (RTDF) to C.N. and from the Hope for Depression Research Foundation (HDRF) to B.S.M. Authors have no conflict of interest.

References

Austin, A.W., et al., 2014. Differential association of insulin resistance with cognitive and somatic symptoms of depression. Diabet. Med. 31 (8), 994–1000.
Bernstein, D.P., et al., 2003. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. Child Abuse Negl. 27 (2), 169–190.
Bigio, B., et al., 2016. Epigenetics and energetics in ventral hippocampus mediate rapid antidepressant action: Implications for treatment resistance. Proc. Natl. Acad. Sci. U. S. A. 113 (28), 7906–7911.
Danese, A., et al., 2009. Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. Arch. Pediatr. Adolesc. Med. 163 (12), 1135–1143.
Daskalakis, N.P., Bagot, R.C., Parker, K.J., Vinkers, C.H., de Kloet, E.R., 2013. The three-hit concept of vulnerability and resilience: toward understanding adaptation to early-life adversity outcome. Psychoneuroendocrinology 38 (9), 1858–1873.
De Felice, F.G., Ferreira, S.T., 2014. Inflammation, defective insulin signaling, and mitochondrial dysfunction as common molecular denominators connecting type 2 diabetes to Alzheimer disease. Diabetes 63 (7), 2262–2272.
Fan, C.A., et al., 2013. The effect of family history of diabetes on sleep quality, depression, and anxiety in adult males with diabetes. J. Diabetes Mellitus 03 (01), 4.
Fletcher, B., Gulanick, M., Lamendola, C., 2002. Risk factors for type 2 diabetes mellitus. J. Cardiovasc. Nurs. 16 (2), 17–23.
Fritz, I.B., McEwen, B.S., 1959. Effects of carnitine on fatty-acid oxidation by muscle. Science 129 (3345), 334–335.
Kenna, H., et al., 2013. Fasting plasma insulin and the default mode network in women at risk for Alzheimer's disease. Neurobiol. Aging 34 (3), 641–649.
Kiraly, D.D., et al., 2017. Altered peripheral immune profiles in treatment-resistant depression: response to ketamine and prediction of treatment outcome. Transl. Psychiatry 7 (3), e1065.
Kullmann, S., et al., 2012. The obese brain: association of body mass index and insulin sensitivity with resting state network functional connectivity. Hum. Brain Mapp. 33 (5), 1052–1061.
Li, L., Garvey, W.T., Gower, B.A., 2017. Childhood maltreatment is an independent risk factor for prediabetic disturbances in glucose regulation. Front. Endocrinol. 8, 151.
Lin, K.W., Wroolie, T.E., Robakis, T., Rasgon, N.L., 2015. Adjuvant pioglitazone for unremitted depression: clinical correlates of treatment response. Psychiatry Res. 230 (3), 846–852.
Lyons, D.M., Parker, K.J., 2007. Stress inoculation-induced indications of resilience in monkeys. J. Trauma. Stress. 20 (4), 423–433.
Lyons, D.M., Parker, K.J., Katz, M., Schatzberg, A.F., 2009. Developmental cascades linking stress inoculation, arousal regulation, and resilience. Front. Behav. Neurosci. 3, 32.
Lyons, D.M., Parker, K.J., Schatzberg, A.F., 2010. Animal models of early life stress: implications for understanding resilience. Dev. Psychobiol. 52 (7), 616–624.
Matsuda, M., DeFronzo, R.A., 1999. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 22 (9), 1462–1470.
McEwen, B.S., 1998. Stress, adaptation, and disease. Allostasis and allostatic load. Ann. N. Y. Acad. Sci. 840, 33–44.
McEwen, B.S., Wingfield, J.C., 2003. The concept of allostasis in biology and biomedicine. Horm. Behav. 43 (1), 2–15.
McEwen, B.S., et al., 2015. Mechanisms of stress in the brain. Nat. Neurosci. 18 (10), 1353–1363.
McEwen, B.S., Nasca, C., Gray, J.D., 2016. Stress effects on neuronal structure: hippocampus, amygdala, and prefrontal cortex. Neuropsychopharmacology 41 (1), 3–23.
McIntyre, R.S., et al., 2009. Metabolic syndrome and major depressive disorder: co-occurrence and pathophysiologic overlap. Curr. Diabetes Rep. 9 (1), 51–59.
Mortimer, J.T., Staff J, 2004. Early work as a source of developmental discontinuity during the transition to adulthood. Dev. Psychopathol. 16 (4), 1047–1070.
Nasca, C., et al., 2017a. ACNP 56th Annual meeting: panels, mini-panels and study groups, December 4–7, 2017. Neuropsychopharmacology 42 (S1).
Nasca, C., et al., 2017b. Role of the astroglial glutamate exchanger xCT in ventral hippocampus in resilience to stress. Neuron 96 (2), 402–413 (e405).
Nasca, C., Rasgon, N., McEwen, B., 2019 Jan. An emerging epigenetic framework of systemic and central mechanisms underlying stress-related disorders. Neuropsychopharmacology 44 (1), 235–236. https://doi.org/10.1038/s41386-018-0227-1.
Nasca, C., et al., 2018 Aug 21. Acetyl-l-carnitine deficiency in patients with major depressive disorder. Proc. Natl. Acad. Sci. U S A. 115 (34), 8627–8632. https://doi.org/10.1073/pnas.1801609115.
Nemeroff, C.B., 2016. Paradise lost: the neurobiological and clinical consequences of child abuse and neglect. Neuron 89 (5), 892–909.
Parker, K.J., Buckmaster, C.L., Sundlass, K., Schatzberg, A.F., Lyons, D.M., 2006. Maternal mediation, stress inoculation, and the development of neuroendocrine stress resistance in primates. Proc. Natl. Acad. Sci. U. S. A. 103 (8), 3000–3005.
Post, R.M., 2018. Myriad of implications of acetyl-l-carnitine deficits in depression. Proc. Natl. Acad. Sci. U. S. A. 115 (34), 8475–8477.
Post RM, et al. (Role of Childhood Adversity in the Development of Medical Co-Morbidities Associated with Bipolar Disorder. (1573–2517 (Electronic)).
Raison, C.L., Capuron, L., Miller, A.H., 2006. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. 27 (1), 24–31.
Rasgon, N., Jarvik, L., 2004. Insulin resistance, affective disorders, and Alzheimer's disease: review and hypothesis. J. Gerontol. 59 (2), 178–183 Series A, Biological sciences and medical sciences. (discussion 184-192).
Rasgon, N.L., McEwen, B.S., 2016. Insulin resistance-a missing link no more. Mol. Psychiatry 21 (12), 1648–1652.
Rasgon, N.L., et al., 2010a. Metabolic dysfunction in women with bipolar disorder: the potential influence of family history of type 2 diabetes mellitus. Bipolar Disord. 12 (5), 504–513.
Rasgon, N.L., et al., 2010b. Rosiglitazone add-on in treatment of depressed patients with insulin resistance: a pilot study. TheScientificWorldJOURNAL 10, 321–328.
Rasgon, N.L., et al., 2011. Insulin resistance and hippocampal volume in women at risk for Alzheimer's disease. Neurobiol. Aging 32 (11), 1942–1948.
Stemmle, P.G., et al., 2009. Insulin resistance and hyperlipidemia in women with bipolar disorder. J. Psychiatr. Res. 43 (3), 341–343.
Tsuno, N., Besset, A., Ritchie, K., 2005. Sleep and depression. J. Clin. Psychiatry 66 (10), 1254–1269.
Watson, K., Nasca, C., Aasly, L., McEwen, B., Rasgon, N., 2018 Jul 1. Insulin resistance, an unmasked culprit in depressive disorders: promises for interventions. Neuropharmacology 136 (Pt B), 327–334. https://doi.org/10.1016/j.neuropharm.2017.11.038.
Williams, L.M., Debattista, C., Duchemin, A.M., Schatzberg, A.F., Nemeroff, C.B., 2016. Childhood trauma predicts antidepressant response in adults with major depression: data from the randomized international study to predict optimized treatment for depression. Transl. Psychiatry 6, e799.
Wroolie, T.E., Kenna, H.A., Singh, M.K., Rasgon, N.L., 2015. Association between insulin resistance and cognition in patients with depressive disorders: exploratory analyses into age-specific effects. J. Psychiatr. Res. 60, 65–72.