Psychiatry Research: Neuroimaging 184 (2010) 63–70

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Regional cortical gray matter thickness differences associated with type 2 diabetes and major depression ☆

Olusola Ajilore[a,*], Katherine Narr[b], Jonah Rosenthal[c], Daniel Pham[c], Liberty Hamilton[b], Kecia Watari[c], Virginia Elderkin-Thompson[c], Christine Darwin[d], Arthur Toga[b], Anand Kumar[a]

[a]Department of Psychiatry, University of Illinois-Chicago, Chicago, IL, United States
[b]Laboratory of Neuroimaging, UCLA, Los Angeles, CA, United States
[c]Department of Psychiatry, UCLA, Los Angeles, CA, United States
[d]Department of Clinical Epidemiology and Preventive Medicine, UCLA, Los Angeles, CA, United States

ARTICLE INFO

Article history:
Received 29 September 2009
Received in revised form 14 July 2010
Accepted 14 July 2010

Keywords:
MRI
Neurocognition
Neuroanatomy
Mood
Diabetes

ABSTRACT

The purpose of this study was to examine the effect of type 2 diabetes with major depression on cortical gray matter using magnetic resonance imaging and cortical pattern matching techniques. We hypothesized that diabetic subjects and depressed diabetic subjects would demonstrate decreased cortical gray matter thickness in prefrontal areas as compared to healthy control subjects. Patients with type 2 diabetes ($n=26$) and patients with diabetes and major depression ($n=26$) were compared with healthy controls ($n=20$). Gray matter thickness across the entire cortex was measured using cortical pattern matching methods. All subjects with diabetes demonstrated decreased cortical gray matter thickness in the left anterior cingulate region. Additionally, depressed diabetic subjects showed significant cortical gray matter decreases in bilateral prefrontal areas compared with healthy controls. Correlations between clinical variables and cortical gray matter thickness revealed a significant negative relationship with cerebrovascular risk factors across all three groups, most consistently in the left dorsomedial prefrontal cortex. A significant positive relationship between performance on attention and executive function tasks and cortical gray matter thickness predominately in left hemisphere regions was also seen across all subjects. Depression and diabetes are associated with significant cortical gray matter thinning in medial prefrontal areas.

1. Introduction

Type 2 diabetes is a significant public health problem associated with a number of devastating sequelae including renal disease, retinal disease and peripheral neuropathy. Due to the microvascular compromise associated with these complications, type 2 diabetes is likely to have deleterious effects on the brain as well. Several studies have probed this idea by examining structural alterations in the brain associated with type 2 diabetes. In a recent review of neuroimaging in diabetes, the authors note several studies demonstrating significant atrophy in cortical and subcortical regions (van Harten et al., 2006). One study cited showed that type 2 diabetes was associated with hippocampal and amygdalar atrophy (den Heijer et al., 2003). A more recent study has demonstrated increased white matter lesions and gray matter atrophy associated with type 2 diabetic subjects when compared to control subjects (Jongen et al., 2007).

In addition to neuroanatomical alterations, major depression can be seen as an associated neuropsychiatric sequela of diabetes. This is evidenced by the notion that major depression and type 2 diabetes are mutual risk factors. There is a large literature examining the relationship between major depression and type 2 diabetes. Prevalence of major depression in a sample diabetic population ranged from 8.5% to 27% according to one study (Gavard et al., 1993). A more recent study reported an age-adjusted prevalence of depression in diabetic patients of 8.3% (95% confidence interval, 7.3% to 9.3%) (Li et al., 2008). Depressed patients have 2.2 times the risk of developing diabetes as compared to non-depressed subjects (Eaton et al., 1996). This bidirectional association was confirmed in a recent analysis using a large, ethnically diverse sample. The presence of major depression has consequences for diabetes in terms of increased rates of hyperglycemia, reduced compliance, diabetic complications, and increased mortality (de Groot et al., 2001; Lustman and Clouse, 2005; Katon et al., 2005).

We have examined the relationship between type 2 diabetes and major depression in a number of domains. Previous work from our group has shown that diabetic subjects (both depressed and non-depressed) had poorer performance on executive functioning tasks compared to healthy control subjects. In addition, compared to healthy control subjects, depressed diabetic subjects had significantly

☆ Presented at the Society for Neuroscience, Washington, DC, November 3–7, 2007.

* Corresponding author. University of Illinois-Chicago, 1601 W. Taylor Street, Chicago, IL 60612, United States. Tel.: +1 312 413 4562; fax: +1 312 996 7658.
E-mail address: oajilore@psych.uic.edu (O. Ajilore).

0925-4927/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.pscychresns.2010.07.003

poorer performance on attention processing tasks (Watari et al., 2006). We have also looked at biochemical differences associated with type 2 diabetes and major depression using magnetic resonance spectroscopy. Diabetic subjects (depressed and non-depressed) had higher myo-inositol concentrations in frontal white matter while depressed diabetic subjects demonstrated lower glutamate/glutamine concentrations in subcortical regions compared to healthy control subjects (Ajilore et al., 2007). Our group has shown that diabetic subjects both with and without depression had lower overall total gray matter volumes and smaller gray matter volumes in anterior cingulate and orbitofrontal regions after controlling for total gray matter (Kumar et al., 2008). Given the deleterious effects of major depression and type 2 diabetes on neurochemistry and cognitive functioning, we wanted to investigate whether these differences were related to structural alterations in the brain focusing on cortical gray matter thickness in the same subject population.

The purpose of this study was to examine the regional neuroanatomical differences associated with both type 2 diabetes and major depression using magnetic resonance imaging. Specifically, since laminar thickness may index pathophysiological processes within the neuropil, we used cortical pattern matching methods to compare cortical thickness at high spatial resolution across the cortex between diagnostic groups. Cortical thickness is considered to be a more reliable measure of gray matter differences compared to volumetric analyses due to decreased structural variability in the cytoarchitecture (Singh et al., 2006). We hypothesized that diabetic subjects and depressed diabetic subjects would demonstrate decreased cortical gray matter thickness in prefrontal areas as compared to healthy control subjects. We also examined the correlations between cortical gray matter thickness and clinical variables (stroke risk, medical co-morbidities, hemoglobin A1c, and diabetes duration). We hypothesized that there would be an inverse relationship between cortical gray matter thickness and these clinical variables. Finally, we examined the correlations between cortical gray matter thickness and two cognitive domains (attention processing and executive function) with the hypothesis that there would be a positive relationship between thickness and performance on tasks related to these two domains.

2. Methods

2.1. Subject selection

We investigated 52 subjects between the ages of 30 and 80, diagnose with type 2 diabetes by their primary care physicians. Type 2 diabetes was diagnosed using established clinical criteria (Mayfield, 1998). Of the 52 subjects with type 2 diabetes, 26 met DSM-IV criteria for major depressive disorder, and 26 subjects denied a history of or current depression and were enrolled as diabetic controls. Subjects were recruited from three outpatient clinical sites: Gonda Diabetes Center at UCLA, UCLA Division of Endocrinology (Santa Monica, CA), and a satellite diabetes clinic (Alhambra, CA). Twenty control participants were recruited through newspaper advertisements circulating in Los Angeles, California. These subjects represent a sample selection whose recruitment details and characteristics have been described in previously published studies from our group (Kumar et al., 2008, 2009; Watari et al., 2006). All subjects were given a structured clinical interview (Structured Clinical Interview for DSM-IV) (Spitzer, 1992) by a trained research associate. Depressed patients received a score of 15 or higher on the Hamilton Rating Scale for Depression (Hamilton, 1960) and none of them had any clinically relevant psychotic features. All patients screened for depression were assessed by a board-certified or board-eligible psychiatrist. All patients diagnosed with major depression were drug-naïve or free of antidepressant medications for at least 2 weeks prior to the study. Diabetic patients were on varying combinations of oral hypoglycemic agents and insulin for blood sugar control. Exclusion criteria for the present study included the following: dementia, central nervous system diseases, unstable medical illnesses, other Axis I disorders (including bipolar disorder), drug or alcohol dependence, or head trauma. Health status and medical co-morbidities were assessed using the Cumulative Illness Rating Scale for Geriatrics (CIRS; (Linn et al., 1968)) and the Cerebrovascular Risk Factor Scale developed by the American Heart Association (CVRF), respectively. To determine glycemic control, hemoglobin A1c (Hgb A1c) levels were measured for all subjects. Subjects also received a neuropsychological battery described in Watari et al. (2006) that included tasks that assessed the cognitive domains of attention and executive function (Watari et al., 2006). The scores were aggregated according to an *a priori* conceptual design into two composite variables: 1) simple attention included visuomotor tracking (Trail Making A) and sustained attention (Stroop, Parts A and B) and 2) executive function included working memory manipulation (Letter–Number Sequences), nonverbal inductive reasoning (Matrix Reasoning), reverse learning (Wisconsin Card Sorting Test), response inhibition (Stroop, Part C), dual attention (Trail Making B), phonetic fluency (Controlled Oral Word Association), and nonverbal design fluency (Ruff Figural Fluency). The aggregated variables showed an acceptable internal validity: Cronbach alphas were 0.80 for executive and 0.78 for attention. All subjects participated with informed consent in accordance with UCLA's Institutional Review Board requirements.

2.2. Image processing

Subjects were scanned with a 1.5-T Signa magnet (GE Medical Systems, Milwaukee).

Images were obtained with the following protocol as a whole-brain, gradient-echo (spoiled gradient recall acquisition) T1-weighted series acquired coronally with section thickness of 1.4 mm, no gaps (repetition time = 20 ms; echo time = 6 ms; flip angle = 45°; field of view = 22 cm; number of excitations = 1.5; matrix size = 256 × 192 mm; in-plane resolution = 0.86 × 0.86 mm).

The image pre-processing has been described in more detail in previous publications (Ballmaier et al., 2004a; Shattuck and Leahy, 2002). In brief, image pre-processing involved whole brain extraction, radiofrequency bias field correction, and automated tissue classification into gray matter, white matter, and CSF using a partial volume correction method (Shattuck et al., 2001). Brain volumes were then transformed into standard stereotaxic space without scaling. From these volumes, the cortical surface was extracted using an automated software resulting in a three-dimensional (3D) model of each hemispheric surface. On the 3D cortical surface model from each subject, 29 sulcal landmarks located throughout the brain were traced for each hemisphere. Interrater variability of manual outlining was measured as the three-dimensional root mean square difference in millimeters between 100 equidistant points from each sulcal landmark traced in six test brains relative to a gold standard arrived at by a consensus of raters. Intrarater reliability was computed by comparing the three-dimensional root mean square distance between equidistant surface points from sulcal landmarks from one test brain traced six times by the same rater. Three-dimensional root mean square disparities were <2 mm, and on average <1 mm, between points for all landmarks within and between raters (Ballmaier et al., 2004a).

Cortical pattern matching methods have been detailed previously (Thompson et al., 2001; Sowell et al., 2004; Narr et al., 2005). Briefly, to align cortical anatomy and allow the measurement of cortical thickness at homologous cortical regions across subjects at high spatial density, the manually-derived sulcal landmarks were used as anchors to drive surface warping algorithms. These cortical pattern matching algorithms create three-dimensional deformation fields that translate each subject's anatomy to the average anatomical pattern from the entire study group. Although the surface anatomy of each subject is not made to conform to the average anatomical pattern of the group, the cortical pattern matching algorithms serve to impose a spatial correspondence between the same anatomical points or