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Alterations in ventral attention network connectivity in individuals with prediabetes

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Abstract

Type 2 diabetes (T2D) is associated with aberrant neural functioning, however the point at which brain function alterations occur in the progression of T2D is unknown. Here, we tested for differences in functional connectivity in adults with prediabetes and healthy individuals. We hypothesized that prediabetes, defined by glycated hemoglobin (HbA_{1c}) 5.7% - 6.4% would be associated with disruptions in default mode network (DMN) connectivity. Fourteen brain networks were tested in 88 adults (prediabetes: n=44; HbA_{1c} = 5.8±0.2%; healthy: n=44; HbA_{1c} = 4.7±0.2%) matched for sex, age, and BMI. We did not find differences in DMN connectivity between groups. Individuals with prediabetes showed stronger connectivity between the ventral attention network and: 1) a visual network (*p*FWE = 0.0001); 2) a somatosensory network (*p*FWE = 0.0027). Individuals with healthy HbA_{1c} showed stronger connectivity of the ventral attention network and: 1) cingulo-opercular network (*p*FWE = 0.002); 2) a thalamic-striatal-visual network (*p*FWE = 0.001). Relative to individuals with prediabetes, those with a healthy HbA_{1c} showed stronger connectivity between brain networks underlying self-control and attention to stimuli. In contrast, those with prediabetes demonstrated stronger connectivity between brain networks associated with sensory and attention to stimuli. While T2D is reported contribute to decreased DMN connectivity, prediabetes is characterized by a shift in functional connectivity from a self-control network towards increasing connectivity in sensory network.

Keywords

functional connectivity; orbitofrontal cortex; prediabetes

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1. Introduction

While best known for hyperglycemia and altered lipid metabolism, type 2 diabetes mellitus (T2D) is also related to symptoms of cognitive decline, including: learning and memory deficits, decreased psychomotor speed, and Alzheimer's disease [1]. Cognitive decline is associated with early symptoms of T2D (e.g., impaired glucose tolerance) and is accelerated in the first years after T2D diagnosis [2]. This indicates that cognitive decline occurs prior to the onset of T2D, likely during the prediabetic state. Prediabetes is a stage of chronically elevated blood glucose above normal, but below the diagnosis of T2D and is generally defined as glycated hemoglobin (a marker of hemoglobin exposure to glucose in prior 2–3 months; HbA_{1c}) between 5.7% to 6.4% [3]. The Centers for Disease Control estimates 33.9% of adults (18 years or older) in the US had prediabetes in 2015 [4] with an average duration of 10 years [5]. This may represent a prolonged, subclinical period of accelerating cognitive decline providing the foundation for cognitive disorders in the future. In support of this thesis, a meta-analysis found that prediabetes was associated with the progression of mild cognitive impairment to dementia [6]. However, it is unknown if this progression is due to poor glycemic control or is a result of additive effects of aging and prediabetes decreasing the threshold at which dementia is symptomatic [2].

Research using functional magnetic resonance imaging (fMRI) on T2D has shown that blood glucose and diabetes-associated cognitive decline are both consistently associated with decreased functional connectivity within the default mode network (DMN) [7, 8]. In contrast with structural connectivity, which represents white matter tracts connecting different brain regions, functional connectivity is defined as coactivation of regions over time [9]. Patients with T2D compared to healthy counterparts, showed deceased activation in regions of the DMN during a working memory task, poorer executive control, and memory abilities [10]. Further, decreased DMN connectivity was seen in the resting state of T2D patients compared to healthy controls [11]. Collectively, this may indicate that altered DMN functioning and connectivity underlies the cognitive dysfunction seen in prediabetes and T2D. Supporting this notion, decreased functional connectivity of the DMN is seen clinical manifestations of cognitive dysfunction such as: mild cognitive impairment, Alzheimer's Disease, multiple sclerosis, and Parkinson's Disease [12]. Additionally, decreased DMN connectivity was negatively correlated with insulin resistance [11], and both cognitive decline and disrupted DMN connectivity were positively associated with HbA_{1c} [8]. The exact physiological mechanism causing DMN dysfunction is unknown, but systemic inflammation related to obesity is a possible cause [13, 14]. Regardless, data indicate that poor glycemic control may aggravate both cognitive decline and DMN connectivity [8]. However, little research has examined changes in functional connectivity and cognitive function before the onset of T2D in prediabetes. In one of the few studies available, van Bussel and colleagues showed a stepwise reorganization of the brain with increasing insulin resistance from prediabetes to T2D, however did not see differences in cognitive dysfunction between prediabetic and healthy group [15]. This suggests neural reorganization may precede cognitive dysfunction in the prediabetic stage [15].

Existing studies indicate that cognitive decline in T2D is a continual process, and may occur before the transition from prediabetes to T2D. However, to date, few studies have focused on

prediabetes, leaving a gap in knowledge about this critical period of neural reorganization and early cognitive decline. Thus, the present study sought to characterize differences in resting state network connectivity in individuals with prediabetes, compared to a sample of healthy individuals that was matched for body mass, sex, and age. We used data from the Human Connectome Project to investigate potential changes in functional connectivity and cognition between healthy subjects and those with prediabetes by virtue of HbA_{1c} status. We hypothesized that compared to those with prediabetes, the healthy individuals will have stronger network connectivity of regions in the DMN.

2. Material and Methods

2.1 Sample selection.

All data was from the Human Connectome Project (HCP) HCP1200-PTN data release [16]. Participants recruited for the HCP gave written informed consent for a protocol approved by the Washington University in St. Louis and University of Minnesota Institutional Review Boards. The data release included 1003 young adults, of which 825 had measurement of HbA1c. Of this group of 825 participants, 45 participants met criteria for prediabetes, defined as $HbA_{1c} > 5.7\%$. One participant was excluded from this group, as their HbA1c was not a plausible measurement (greater than 3 standard deviations above than the mean), otherwise, there was no upper limit for HbA_{1c}. The final sample included 44 individuals with prediabetes. No participants reported use of diabetic medication. For comparison, 44 individuals were selected from the sample of 780 individuals with healthy HbA_{1c}. The healthy group was selected by matching BMI, age, and sex to the prediabetes group. Selection was done by a researcher blinded to HbA_{1c} values. Sample characteristics are described in Table 1.

2.2 Data description and preprocessing.

Data collection, preprocessing, and analysis for the PTN release in the Human Connectome Project has been detailed extensively elsewhere [17], therefore it will only be summarized here. Participants completed 4 resting state functional MRI (rfMRI) runs, totaling 58 minutes and 12 seconds of rfMRI data per participant [16]. Each rfMRI scan was performed on a 3 Tesla Siemen's Skyra magnet and used an eight-factor multiband, gradient echo EPI sequence with the following parameters: TR: 720ms, TE: 33.1ms, flip angle: 52 degrees, slice thickness: 2.0mm [16]. During the rsfMRI scan, participants were instructed to look at a light crosshair on a dark background projected into their field of view. The Human Connectome Project preprocessed all downloaded data in the HCP1200-PTN release using the recommended minimal preprocessing pipeline [18], and no additional preprocessing was performed locally.

2.3 Group ICA.

The Incremental Group-Principle Components Analysis (PCA) tool from the Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) software [19] (Version 3.0, FMRIB, Oxford, UK) was used to generate dense connectomes of all participants' individual timeseries and then parcellated using group-Independent Components Analysis (ICA) to create 15 spatial-ICA network maps. Multiple components

in a given network map may include the same anatomical region, therefore components will be referred to as independent components (ICs) with their number and anatomical region(s) comprised within e.g., occipital pole (IC 9) relative to occipital pole (IC 3). Two researchers independently identified noise components, with an inter-rater reliability of 93%. In the case of disagreement, the researchers reached consensus through discussion. Components were flagged as noise when BOLD activity was primarily following the gyri and/or solely following the surface of brain/skull [20]. As a result, component 9 was determined to be noise and was removed from consideration.

2.4 Individual component timeseries and creation of netmats.

Individual participant timeseries were concatenated and spatially mapped to the corresponding network map described above. The group network maps were each regressed against the corresponding individual component timeseries using dual regression to create individual participant network matrices (netmats) representing activity in the IC networks over time.

2.5 Statistical analyses.

FSLNets (Version 0.6, FMRIB, Oxford, UK) was used to assess group differences between RSN connectivity. Network activity represented in netmats (described above) were correlated over time with normalized covariances resulting in individual correlation matrixes representing pairwise correlations between all IC networks. In the final step of FSLNets analysis, a paired T-test was performed on the correlation matrices to compare connectivity between the two groups. Results were viewed under the following contrasts: 1) stronger connectivity in the prediabetes group compared to healthy group (prediabetes > healthy), and 2) stronger connectivity in the healthy group compared to prediabetes group (healthy > prediabetes). To correct for potential false positives, non-parametric permutation testing was used through FSL's Randomise tool with 10,000 permutations. Results were considered significant at $p_{FWE} < 0.05$. Negative correlations were not included in analyses, as they are not interpretable in the present context [21].

Metrics of cognitive performance were also compared between the prediabetes and healthy groups. Nine measures were considered: Dimensional Change Card Sort Test, Picture Sequence Memory Test (Age-Adjusted), Flanker Inhibitory Control and Attention Test (Age-Adjusted), Penn Progressive Matrices: Number of Correct Responses, Pattern Comparison Processing Speed Test (Age-Adjusted), Picture Vocabulary Test (Age-Adjusted), and Delay Discounting: Area Under the Curve for $200 and $40,000 [22]. To test for significant differences in each metric between the prediabetes and healthy HbA_{1c} groups, Welch's T-tests were used. Significance was considered at a Bonferroni-corrected significance threshold of $p < 0.0056$. Non-imaging analysis were performed using R (v.3.3.2, The R Foundation for Statistical Computing). Preregistration and analytic scripts for this study can be found via the Open Science Framework (Center for Open Science, Charlottesville, VA, USA, DOI 10.17605/osf.io/aqx9c). All scripts for this analysis can be found on Github at https://github.com/niblunc/prediabetes_HCP_paper.

3. Results

3.1 Sample characteristics.

Participant demographics can be found in Table 1. The prediabetes group (n=44) had an average HbA_{1c} of 5.8 ± 0.2%, while the healthy HbA_{1c} group (n=44) had an average HbA_{1c} of 4.7 ± 0.2%; the difference in HbA_{1c} between groups was significant (t= 29.8, $p < 0.0001$). The two groups also significantly differed in racial distribution ($\chi^2 = 14.4$, $p = 0.01$), with the prediabetes group containing a higher proportion of self-identified minority participants than the healthy HbA_{1c} group. The two groups did not significantly differ in sex, age, BMI, or ethnicity (p's = 0.13 – 1.0).

3.2 Network connectivity associated with prediabetes.

Compared to the healthy HbA_{1c} group, prediabetes was associated with stronger connectivity of the ventral attention network including the lateral orbitofrontal cortex (lOFC)/middle temporal gyrus (IC12) with: 1) a visual network comprising the occipital pole (IC 3; t= 4.28; $p_{FWE} = 0.0001$); and with 2) a somatosensory network containing precentral and postcentral gyrus (IC 11; t= 4.20; $p_{FWE} = 0.0027$; Figure 1).

3.3 Network connectivity associated with healthy HbA_{1c}.

Compared to the prediabetes group, the healthy HbA_{1c} group showed stronger connectivity of the ventral attention network (IC12) with: 1) cingulo-operecular task control network including the insula, cingulate, middle frontal gyrus, superior temporal gyrus (IC 7; t= 4.15; $p_{FWE} = 0.0024$); and with 2) thalamic and striatal/visual network (IC 8; t= 4.38; $p_{FWE} = 0.0011$). Additionally, stronger connectivity between the thalamic and striatal/visual network (IC 8) and the somatosensory cortex including the precentral gyrus and insula (IC 13; t= 5.21; $p_{FWE} < 0.0001$; Figure 2).

3.3 Between-group differences in cognitive performance metrics.

Significant differences between the healthy HbA_{1c} and prediabetes groups were observed on two measures of cognitive performance: the Dimensional Change Card Sort Test ($\bar{x}$-prediabetes: 115.4, $\bar{x}$-healthy: 100.6, t=6.4, $p_{FWE} < 0.0001$) and the Picture Vocabulary Test ($\bar{x}$-prediabetes: 102.7, $\bar{x}$-healthy: 112.5, t=2.9, $p_{FWE} < 0.0049$). There were no significant differences between the prediabetes and healthy HbA_{1c} groups in age-adjusted metrics of cognitive performance including: Picture Sequence Memory Test (Age-Adjusted), Flanker Inhibitory Control and Attention Test (Age-Adjusted), Penn Progressive Matrices: Number of Correct Responses, Pattern Comparison Processing Speed Test (Age-Adjusted), and Delay Discounting: Area Under the Curve for Discounting of $200 and $40,000. A summary of behavioral results can be found in Table 3.

4. Discussion

The present study sought to identify differences in brain network connectivity between two samples: individuals with prediabetes and BMI/sex/age-matched individuals with healthy HbA_{1c}. We hypothesized that prediabetes would be associated with alterations to connectivity of the DMN, which previously was shown to be disrupted in T2D [7, 23].

While we did not see a difference in the DMN, we observed that prediabetes was associated with stronger connectivity between the ventral attention network (including the OFC) with a visual network and a somatosensory network. Conversely, healthy HbA_{1c} was related to connectivity between the aforementioned ventral attention network to the cingulo-opercular task network, which includes the insula and dlPFC. We observed that healthy HbA_{1c} was also related to stronger connectivity between the ventral attention network with a network including the thalamus, ventral striatum, and visual cortex. Lastly, the thalamic-striatal-lingual network had a significantly stronger connection to a somatosensory network including the precentral gyrus and insula (Figure 3).

The ventral attention network is comprised of the OFC and middle temporal gyrus and is shown to be insulin sensitive [24]. This network showed significant connectivity in both the groups, however it was differentially connected between samples. Specifically, the individuals with prediabetes showed increased connectivity between the ventral attentional network and the occipital pole and the somatosensory cortex. Research with healthy subjects has shown that responses in the occipital cortex and OFC have an inverse relationship to plasma insulin [25]. An insulin resistant state, such as prediabetes, is associated with decreased insulin sensitivity in the occipital pole and OFC, potentially predisposing individuals with insulin resistance to increased attention to food cues [24, 25]. Increased connectivity between the ventral attention network and occipital pole may result in a similar attentional bias to food cues in the prediabetes group. Additionally, the ventral attention network in the group with prediabetes showed increased connectivity to the somatosensory cortex. The somatosensory cortex is responsive to food intake [26], and shows sensitivity to insulin [25]. Similar to the present finding, in a sample of adolescents, increasing insulin resistance was associated with increased BOLD response to a sweet, high calorie beverage in the lOFC, middle temporal gyrus, and occipital cortex [25]. The similarity between task response and resting state may indicate that in the prediabetic state, the resting brain shows connectivity similar to ingesting a sweet beverage. Insulin resistance, or a poor glycemic control cognitive state, where the brain no longer responds to the homeostatic signaling could drive this pattern of response. Further, the lack of connectivity to the cingulo-operecular task control network in the group with prediabetes may additionally provide evidence for a neural shift away from self-regulating brain areas, as seen previously [27], and instead toward sensory brain regions. Decreased connectivity within the cingulo-opercular task control network has been seen in T2D patients and was correlated with illness duration [8]. Together this indicates the cingulo-opercular network may be sensitive to insulin resistance and/or poor glycemic control, and with further disease progression, this area decreases inter- and intra-network connectivity.

Healthy HbA_{1c} was associated with increased connectivity between the thalamic-striatal-visual network to the somatosensory cortex and the ventral attention network. Previously, increased connectivity of the striatum and somatosensory areas was found in adolescents with excess weight [28]. The previous sample was overweight but metabolically healthy, similar to the healthy HbA_{1c} sample in the present analysis. Decreased glycemic control, controlling for BMI, may result in a diminished thalamic-striatal-visual to somatosensory connection, instead favoring the ventral attention to somatosensory relation. Additionally, healthy HbA_{1c} was associated with stronger ventral attention network and thalamic-striatal

connectivity. Together, this pattern of connectivity is representative of a cortical-striatal-thalamic loop implicated in cognitive control, decision-making, and reversal learning [29]. Pre-clinical models have shown that greater thalamic-cortical and cortical-striatal associations may be related to increased top-down behavioral control [30]. In conjunction with the increased connectivity of the cingulo-opercular network to the ventral attention network, this overall suggests an increased top-down behavioral control network in the healthy HbA_{1c} group compared to the prediabetic group.

The similarity in DMN connectivity between the two groups may indicate that degradation of the DMN seen in T2D [7] occurs with worse glycemic control or longer disease duration than is present in the current prediabetes sample. In support, the samples in prior research had HbA_{1c} levels over 20% higher than the present study [7]. Another possibility is a difference in the DMN effect is a function of duration of elevated HbA_{1c}. The populations in the previous studies may have had elevated HbA_{1c} levels for a longer period of time, resulting in increased complications. Longer duration of T2D is considered a risk factor for development of peripheral neuropathy [31], and may also be related to decreased DMN connectivity [23]. Further, the DMN connectivity is shown to be sensitive to systemic inflammation [14]. While inflammation is elevated in prediabetes, obesity is most often implicated in the inflammatory state [32]. Since the present sample was matched on BMI, variation in obesity-induced systemic inflammation and corresponding changes to DMN connectivity may be diminished. Therefore, alterations to DMN connectivity may be associated with a longer duration, poorer glycemic control, and greater weight disparity between groups than our sample exhibited.

The two samples showed, inconsistent, yet significant differences in metrics of behavioral cognitive performance. Those with prediabetes had lower performance on the Picture Vocabulary Test, a measure of receptive vocabulary. However, the group with prediabetes performed better on the Dimensional Cart sort task, which is a measure of cognitive flexibility. Despite evidence for cognitive deficits in T2D [2], the observed differences between the two samples, are likely not clinically meaningful. The average score in each sample was at or above the median age-adjusted score on either task, suggesting that despite comparative differences, no deficits in cognitive function were found in either sample [33]. A lack of clinically meaningful cognitive differences was also seen between healthy participants and participants with prediabetes previously, further indicating that changes in functional organization of the brain may occur before the onset of cognitive impairment [15]. An additional caveat could be duration of prediabetes. A limitation of this data is we are unable to model duration of having prediabetes, which may account for variability in cognitive dysfunction [34]. Also, while the samples were matched for BMI, age, and sex, there was a significant difference in racial distribution between the two samples. The prediabetes group had a higher proportion of minority individuals, which is unsurprising as minority individuals are at higher risk of developing prediabetes and type 2 diabetes [1].

5. Conclusions

In sum, the data presented here support that prediabetes is associated with distinct alterations to network connectivity of the ventral attention network, independent of BMI, age, or sex

differences. These changes may reflect a cognitive insulin resistance, shifting the brain from task control networks towards sensory networks.

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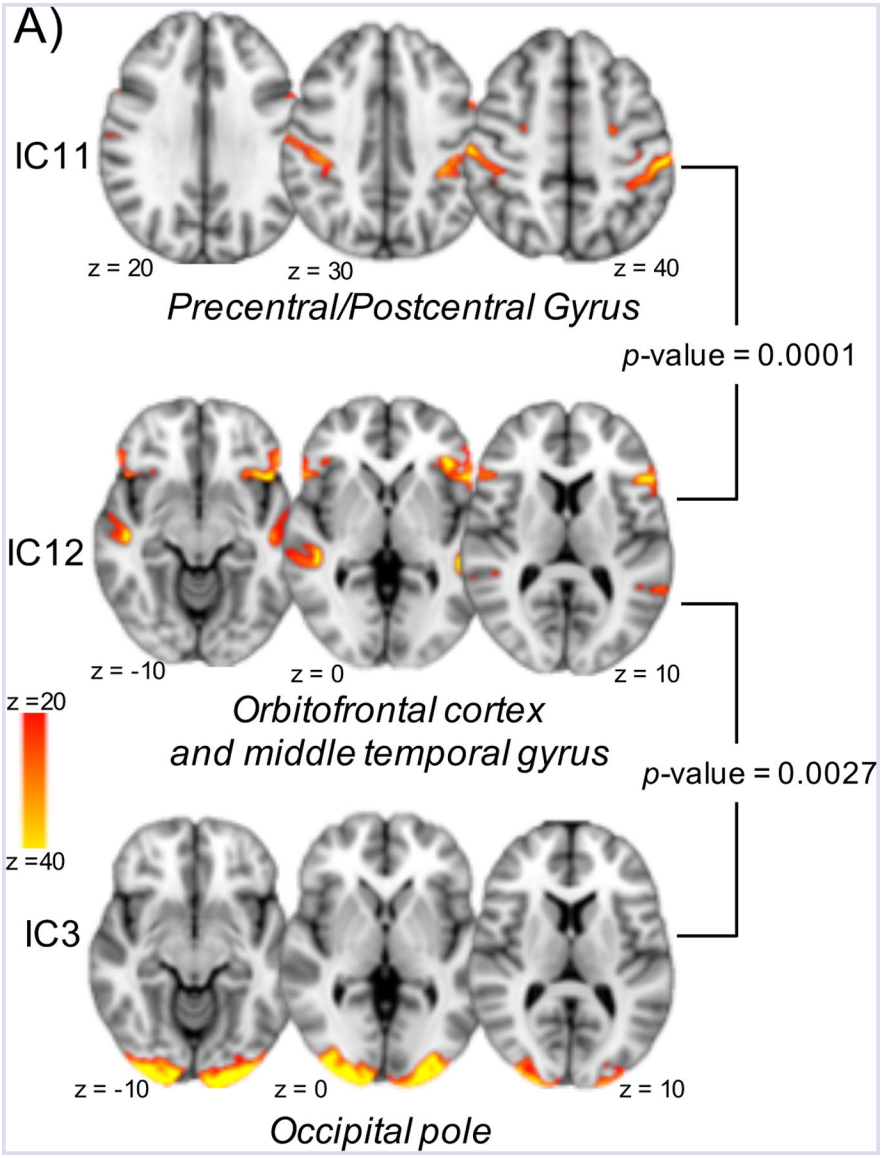

Figure 1:

A) Prediabetes was associated with stronger connectivity of the orbitofrontal cortex/middle temporal gyrus (IC12) with 1) a somatosensory network containing precentral and postcentral gyrus (IC 11; t= 4.20; p_{FWE} = 0.0027); and 2) a visual network comprising the occipital pole (IC 3; t= 4.28; p_{FWE} = 0.0001); compared to individuals with healthy HbA_{1c}.

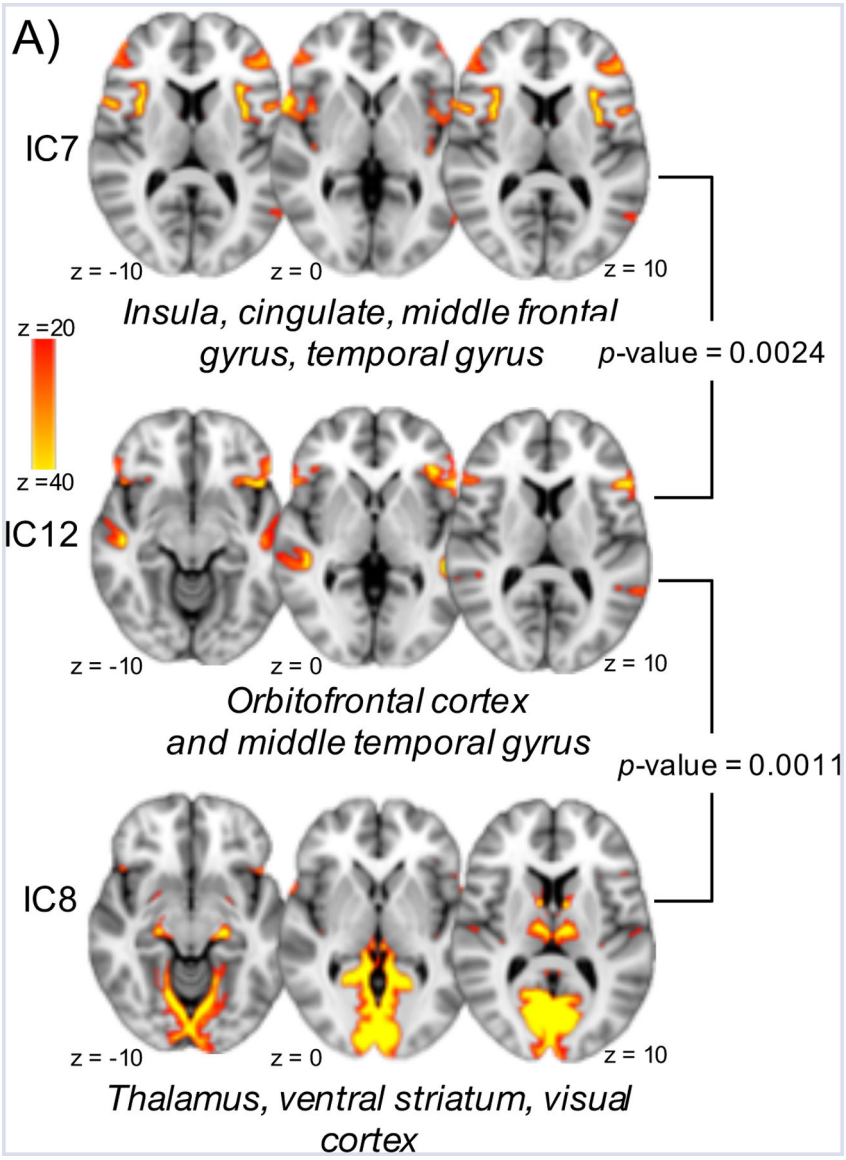

Figure 2:

A) Compared to the prediabetes group, healthy HbA_{1c} was associated with stronger connectivity of OFC/middle temporal gyrus (IC12) with 1) the insula, cingulate, middle frontal gyrus, superior temporal gyrus (IC 7; t= 4.15; p_{FWE} = 0.0024); and with 2) a network including the thalamus, ventral striatum, and visual cortex (IC 8; t= 4.38; p_{FWE} = 0.0011).

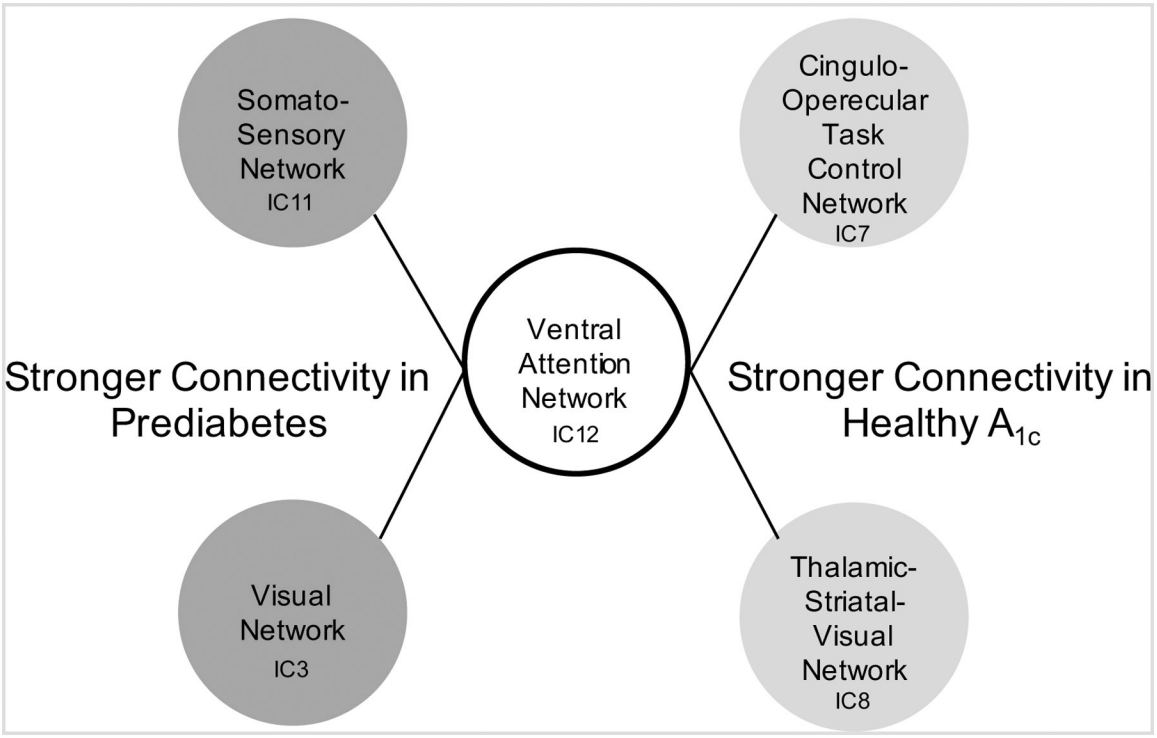

Figure 3:
Simplified representation of network connectivity associated with prediabetes and healthy HbA_{1c}.

Table 1:

Sample Characteristics

	Healthy Group (N=44)	Prediabetes Group (N=44)	*p*-value[a]
Sex	M: 18 F: 26	M: 18 F: 26	1.0
Age (years)	28.3 ± 3.6	29.0 ± 4.4	0.37
Body Mass Index (kg/m^2)	26.6 ± 3.3	28.1 ± 5.8	0.13
Race			
Caucasian	37 (84.1%)	22 (50.0%)	0.013*
African American	3 (6.8%)	13 (29.5%)	
Asian or Pacific Islander	1 (2.3%)	5 (11.4%)	
Native American/American Indian	0 (0%)	1 (2.3%)	
More than one race	2 (4.5%)	1 (2.3%)	
Unknown	1 (2.3%)	2 (4.5%)	
Ethnicity			
Hispanic	2 (4.5%)	6 (13.6%)	0.21
Non-Hispanic	41 (93.2%)	38 (86.4%)	
Unknown	1 (2.3%)	0 (0%)	
Hemoglobin A_{1c}	28 ± 0.6 mmol/mol 4.7 ± 0.2%	40 ± 0.6 mmol/mol 5.8 ± 0.2%	< 0.0001*

[a] significant testing between groups was completed using Welch two sample t-test or Pearson's chi-squares test. Significance is considered at $p < 0.05$. Significant differences are denoted with an asterisk (*)

Table 2:

Network connectivity differences in diabetes and healthy HbA_{1c} groups

Prediabetes Group > Healthy HbA_{1c} Group			
Connected Networks (Component #)		***t-value***	***p-value***
Lateral orbitofrontal cortex and middle temporal gyrus (12)	Occipital pole (3)	4.28	0.0001
Lateral orbitofrontal cortex and middle temporal gyrus (12)	Precentral gyrus (11)	4.20	0.0027
Healthy HbA_{1c} Group > Prediabetes Group			
Connected Networks (Component #)		***t-value***	***p-value***
Lateral orbitofrontal cortex and middle temporal gyrus (12)	Insula, dorsolateral prefrontal cortex, precuneus (7)	4.15	0.0024
Lateral orbitofrontal cortex and middle temporal gyrus (12)	Thalamus, ventral striatum, lingual gyrus (8)	4.38	0.0011
Thalamus, ventral striatum, lingual gyrus (8)	Postcentral gyrus and insula (13)	5.21	<0.0001

Table 3:

Between-Group Test of Behavioral Characteristics

Test	Range of Possible Scores	Healthy Group (N=44)	Prediabetes Group (N=44)	*t-value*	*p*-value[a]
Delay Discounting: Area Under the Curve for Discounting of $200	0.0–1.0	0.24 ± 0.15	0.25 ± 0.22	0.16	0.87
Delay Discounting: Area Under the Curve for Discounting of $40,000	0.0–1.0	0.54 ± 0.28	0.46 ± 0.32	1.24	0.22
Dimensional Change Card Sort Test	80–145	100.57 ± 11.82	115.37 ± 9.52	6.42	< 0.0001*
Flanker Inhibitory Control and Attention Test (Age-Adjusted)	75–125	99.33 ± 7.74	102.76 ± 10.21	1.78	0.08
Pattern Comparison Processing Speed Test (Age-Adjusted)	75–125	106.5 ± 18.58	100.2 ± 26.81	1.28	0.20
Penn Progressive Matrices: Number of Correct Responses	0–24	16.67 ± 4.41	15.19 ± 5.3	1.42	0.16
Picture Sequence Memory Test (Age-Adjusted)	55–135	107.66 ± 14.35	102.59 ± 16.31	1.55	0.12
Picture Vocabulary Test	85–155	112.53 ± 13.1	102.67 ± 18.42	2.89	0.004*

[a] significant testing between groups was completed using Welch two sample t-test. Significance is considered at Bonferroni corrected $p < 0.005$. Significant differences are denoted with an asterisk (*)