Brain Glucose Metabolism and Aging: A 5-Year Longitudinal Study in a Large Positron Emission Tomography Cohort

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Brain glucose metabolism, assessed by ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET), can be used to quantify neuronal activity in the human brain (1). Aging is accompanied by a decrease in brain glucose metabolism in frontal, temporal, and parietal lobes. In addition to aging, brain glucose uptake depends on metabolic variables (2). BMI is negatively associated with brain glucose metabolism in prefrontal cortex and cingulate gyrus, while negative associations with blood glucose level are observed in posterior cingulate gyrus and occipital cortex.

The reported effects of aging and metabolic variables on brain glucose metabolism have been inconsistent across studies, possibly due to the limited statistical power and cross-sectional study designs. To resolve the effects of aging, as well as metabolic and psychological factors on brain glucose utilization, we analyzed a large cohort of healthy middle-aged adults who underwent a health checkup program twice: at baseline and at the 5-year follow-up. We used Bayesian hierarchical modeling to estimate the effects of clinical variables on brain glucose metabolism.

We retrospectively analyzed data from 441 healthy males (mean age 42.8 years, range 38–50 years). The health checkup program included ^{18}F-FDG PET, anthropometric and body composition measurements, blood pressure, blood samples, and questionnaires pertaining to mental health. Static PET scans were acquired 60 min after injection of ^{18}F-FDG. The standardized uptake value ratio (SUVR) was calculated from the mean uptake of the region of interest scaled with the mean global cortical uptake. Hierarchical clustering analysis for the predictor variable set defined 5 clusters: *1*) metabolic variables (BMI, waist-to-hip ratio, fat percentage, −1∗ muscle percentage, and HOMA of insulin resistance): *2*) blood pressure (systolic and diastolic): *3*) glucose (fasting glucose and HbA_{1c}): *4*) psychological well-being (stress and depression): and *5*) heart rate. The effects of these clinical variable clusters on regional SUVR were investigated using Bayesian hierarchical modeling.

All the clinical variables changed during the follow-up except for depression score. Stress score and muscle percentage ($P < 0.0001$) decreased while other variables increased ($P < 0.0001$). Comparison between the baseline and follow-up SUVRs is shown in Fig. 1*A*. SUVRs decreased in the caudate, cingulum, and frontal and parietal lobes ($P < 0.0001$) and increased in the cerebellum, hippocampus, putamen, pallidum, thalamus, and occipital and temporal lobes ($P < 0.05$). SUVR in insula ($P = 0.6975$) remained unaltered. Baseline and follow-up SUVRs were strongly correlated (Fig. 1*B*).

The effects of clinical variables on SUVRs were similar in the baseline and follow-up scans. Metabolic variables were negatively associated with SUVR in the thalamus, pallidum, hippocampus, putamen, and parietal lobe and positively with SUVR in the frontal lobe. The effects of glucose on SUVRs varied across regions. The association was positive in the hippocampus, caudate, temporal lobe, and cerebellum and negative in cingulum and occipital, parietal, and frontal lobes. The effects of blood pressure and psychological variables overlapped zero in most regions. However, a negative association between psychological well-being and SUVR was found in thalamus and hippocampus in follow-up, while heart rate was positively associated with SUVRs in the thalamus, hippocampus, cingulum, and cerebellum and negatively with SUVR in the occipital lobe (Fig. 1*C*).

The annual decline of brain glucose metabolism was ∼0.2% across the regions, which is in accordance with that of older adults (3). Our results highlight a clear shift in glucose utilization from frontoparietal to occipitotemporal lobes and limbic area lobes. Decreased brain glucose metabolism in the frontal lobe is related to cognitive decline in normal aging. In turn, a relative increase of brain

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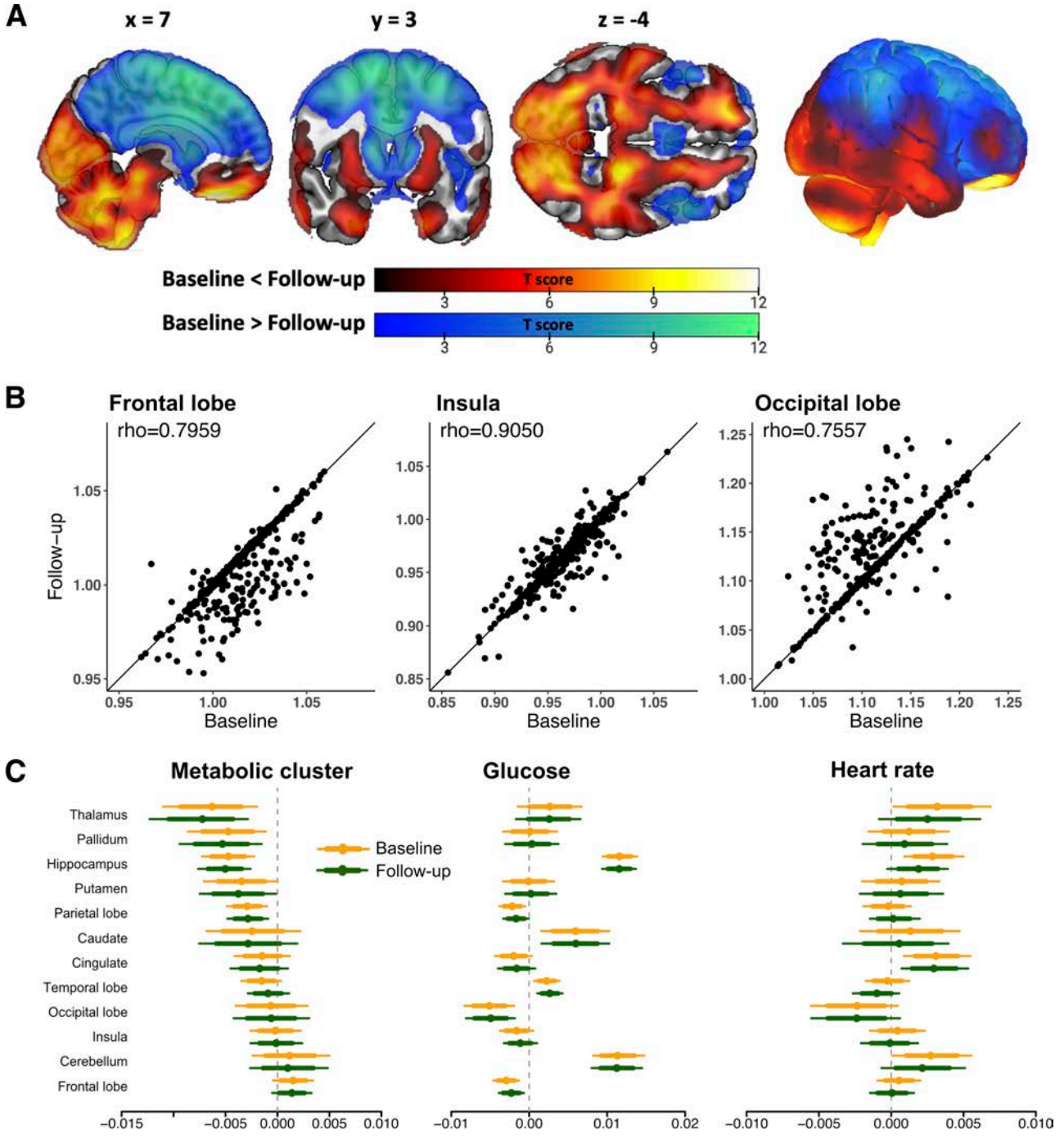

Figure 1—*A*: Full-volume comparison between baseline and follow-up ^{18}F-FDG PET scans. *B*: Distribution of SUVRs of frontal lobe, insula, and occipital lobe in baseline and follow-up ^{18}F-FDG PET scans. *C*: Posterior intervals of the regression coefficients for metabolic cluster, glucose, and heart rate for prediction of SUVR. The thick lines represent the 80% posterior intervals, the thin lines represent the 95% posterior intervals, and the circles represent posterior means.

glucose metabolism in the cerebellum, temporal lobe, and striatum and limbic regions might be associated with compensatory visual/motor activity resulting from decreased activity in the default mode network (4).

The association between metabolic variables and brain glucose metabolism may be linked to Alzheimer's disease, as high BMI and low-muscle area are associated with cognitive decline. The association between blood glucose level and decreased brain glucose metabolism might reflect a characteristic pattern of Alzheimer's disease and neuronal injury before the onset of cognitive impairment (5). The association between psychological variables (stress and depression) and brain glucose metabolism became prominent at the 5-year follow-up: thus, depression and stress may begin to affect brain glucose metabolism after individuals have reached their mid-40s, when the allostatic load has accumulated for a long time.

In conclusion, brain glucose utilization begins to shift from frontoparietal to occipitotemporal lobes and limbic areas in

middle age, while individual differences in brain glucose metabolism remain stable. Metabolic variables, glucose, and heart rate had regionally specific associations with brain glucose metabolism. These effects remained consistent over the 5-year follow-up in middle adulthood, suggesting that glucose utilization starts declining during middle age.

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