parietotemporal metabolic deficit due to the small cerebellar reduction. The result reported by Ishii et al. (*1*) is consistent with our findings in this regard. However, when estimating significance of the parietotemporal reduction with statistical estimates accounting for both the magnitude and variance, the estimate was greater with cerebellar normalization (t = 8.09 without normalization, t = 10.5 with normalization). The benefit of data normalization for the diagnostic application was also tested prospectively (*4*). This indicates that data normalization can be as beneficial in reducing variability in quantitative data as in providing a reference for nonparametric measures particularly when the purpose of normalization is to localize metabolic changes associated with diseases.

A potential bias could also be found in the results presented by Ishii et al. (*1*). Because of the definition of ratio B (*1*), even when a mean cerebellar cerebral metabolic rate for glucose (CMRglc) in AD remains the same as that in normal controls, individual variability in cerebellar CMRglc in AD results in mean ratio B being larger than mean ratio A. Thus, the comparison of ratio A and ratio B is biased toward ratio A being relatively smaller by the definition itself. Greater variability in cerebellar metabolism, not only a decrease in mean cerebellar metabolism, may be a contributing factor in greater differences in their indices in advanced AD patients. Alternatively, the authors could calculate a denominator of ratio B as mean (parietal CMRglc/cerebellar CMRglc) of 13 normal controls, which would be more appropriate for comparison with ratio A.

It is intuitively obvious that if CMRglc in a reference region decreases, the magnitudes of normalized CMRglc reductions in sample regions will be underestimated. This is particularly a concern in advanced AD patients (*1,2*), although application of cerebellar normalization in functional brain imaging of mild or early AD would still be appropriate. In fact, these are the patients we are most interested in to study in research as well as clinical settings. It is, of course, important to keep in mind that normalized CMRglc represents relative metabolic activity and does not simply replace careful quantitative experiments of functional brain imaging (*5*). Cerebellar metabolic abnormality in AD has not been emphasized in the past. Akiyama et al. (*6*) previously reported an autopsy correlation with antemortem PET findings of cerebellar metabolic abnormality in AD, suggesting potential remote effects. Primary pathology also occurs in the cerebellum (*7*). The pathophysiology and significance of such findings are yet to be determined.

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REPLY: We thank Minoshima et al. for their interest in our article (*1*). In our article, we tried to emphasize the pathophysiological feature of Alzheimer's disease (AD), in which even the cerebellum would be affected in the advanced stage. Therefore, Minoshima et al.'s argument is outside of our focus and is somewhat misleading.

TABLE 1
Regional Cerebral Glucose Metabolism in Each Group

	Basal ganglia	Thalamus	Pons
Severe AD	7.14 ± 0.94*	6.58 ± 1.04*	4.57 ± 0.40
Moderate AD	7.82 ± 1.06	7.21 ± 1.15	4.81 ± 0.72
Mild AD	8.18 ± 1.21	7.63 ± 1.20	5.00 ± 0.74
Normal	8.48 ± 1.31	7.63 ± 0.87	5.22 ± 0.57

*Significantly different from normal control values ($p < 0.05$).
AD = Alzheimer's disease.

We completely agree with their opinion that normalization of the intersubject difference of metabolic rate is effective in studies and evaluation of AD, and in fact, we have used a normalization technique in forthcoming articles (*2–4*). However, it is also true that there is no perfect reference region for normalization in the brain affected by AD. This implies that, in an intersubject normalization by any region, the severity of the disease is potentially factored in. Any of the regions insusceptible to AD pathology, including the cerebellum, occipital lobe, sensorimotor cortex, basal ganglia, thalamus and pons, can be used as a reference for normalization with little overcorrection when patients with mild or early AD are the subjects, whereas normalization using such regions is subject to overcorrection when the subjects include those with advanced AD. The relatively important issue is what region is preferable for normalization for studies of AD.

Insusceptibility of the structure and reliability of the measurement are prerequisite for a reliable normalization reference. We supplemented our study by measuring the cerebral metabolic rate for glucose (CMRglc) in the basal ganglia, thalamus and pons (Table 1). The mean values of CMRglc in the basal ganglia and in the thalamus were significantly decreased in severe AD as compared with those in normal controls. Although the difference in the mean pontine CMRglc was not significant among groups, the mean pontine CMRglc in the severe AD group decreased to 88% of that in normal subjects. Therefore, in terms of the region unaffected in AD, the correction by the pontine metabolic rate seems to be advantageous. However, as the measurement was usually not repeated or averaged because of its small size, the reliability of the measurement would be low.

We used an experiment evaluating the test–retest reliability, in which two investigators separately measured CMRglc in the pons and sensorimotor area in 15 subjects (AD patients and normal controls). We compared the reproducibility of measurement in the pons with that in the sensorimotor area. Two regions of interest (ROIs) in the pons and eight ROIs in the bilateral sensorimotor strip were placed, and the metabolic rate in each region was represented as the mean value of the ROIs. The intraclass correlation coefficients were 0.82 for the pons and 0.95 for the sensorimotor strip. The mean differences between the two measures were 1.09% ± 0.95% and 0.96% ± 0.57% for the pons and sensorimotor strip, respectively. In addition, the low baseline value of the metabolic rate (about two-thirds of the cortical rates), when used as the denominator in the normalization process, may cause a large variability. An error of measurement would be amplified by 1.5 times. We prefer a normalization using the primary sensorimotor area as a reference region to analyze CMRglc in patients with mild-to-moderate AD because of the higher value and more reliable measurement in this region.

Finally, Minoshima et al. pointed out a problem in our method for calculating ratio B (*1*). The method they suggested seems more appropriate than our original one, although the expected changes are small. We recalculated the ratio B according to their suggestion and found that all the revised values were quite similar to the original ones, and that the overall results remained unchanged.

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