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ORIGINAL ARTICLE

Upper cerebellar glucose hypermetabolism in patients with temporal lobe epilepsy and interictal psychosis

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Abstract

Objective: Psychosis is an important comorbidity in epilepsy, but its pathophysiology is still unknown. The imaging modality ^{18}F-fluorodeoxyglucose-positron emission tomography (^{18}F-FDG PET) is widely used to measure brain glucose metabolism, and we speculated that ^{18}F-FDG PET may detect characteristic alteration patterns in individuals with temporal lobe epilepsy (TLE) and psychosis.

Methods: We enrolled 13 patients with TLE and interictal psychosis (TLE-P) and 21 patients with TLE without psychosis (TLE-N). All underwent interictal ^{18}F-FDG-PET scanning. Statistical Parametric Mapping (SPM)12 software was used for the normalization process, and we performed a voxel-wise comparison of the TLE-P and TLE-N groups.

Results: Cerebral hypometabolic areas were observed in the ipsilateral temporal pole to hippocampus in both patient groups. In the TLE-P group, the voxel-wise comparison revealed significantly increased ^{18}F-FDG signals in the upper cerebellum, superior cerebellar peduncle, and midbrain. There were no significant between-group metabolic differences around the focus or other cerebral areas.

Significance: Our results demonstrated significant hypermetabolism around the upper cerebellum in patients with TLE and interictal psychosis compared to patients with TLE without psychosis. These findings may reflect the involvement of the cerebellum in the underlying neurobiology of interictal psychosis and could contribute to a better understanding of this disorder.

KEYWORDS

^{18}F-FDG PET, brain metabolism, interictal psychosis, temporal lobe epilepsy

1 | INTRODUCTION

Psychiatric comorbidity is a crucial problem for patients with epilepsy.[1] It is well known that there a much higher prevalence of psychiatric disorders among individuals with epilepsy compared to the general population,[2] and such psychiatric disorders significantly affect their quality of life.[3,4] The relationship between epilepsy

and psychiatric comorbidity is complex. In addition to the high prevalence of psychiatric disorders in individuals with epilepsy, psychiatric symptoms sometimes occur prior to the onset of epilepsy and are correlated with seizure outcomes.[5] We have thus speculated that there may be a bidirectional relationship between epilepsy and psychiatric disorders. Investigations of the underlying pathophysiology may not only lead to better treatments and quality of life for individuals with epilepsy but also deepen our biological knowledge of epilepsy itself.

Psychosis is a severe psychiatric status that often presents with hallucination and/or delusion,[6] and, according to a systematic review, the odds ratio for psychosis is 7.8 times higher in individuals with epilepsy than in the general population.[7] The underlying mechanism of the high comorbidity of epilepsy and psychosis is still unclear, although several potential neural systems, including brain structure, neurotransmitters, and immune system have been suggested.[5]

Neuroimaging is a powerful tool for noninvasive investigations of the brain, and there have been substantial applications of high-resolution structural magnetic resonance imaging (MRI) and functional imaging for neuropsychiatric disorders. Regarding neuroimaging studies of psychosis with epilepsy, the results of structural MRI studies have been relatively heterogeneous and inconsistent.[8] More recently, bilateral hippocampal tail atrophy,[9] abnormal brain aging,[10] and structural network abnormalities were observed in studies of epilepsy.[11,12] In contrast to structural MRI studies, functional imaging studies on psychosis with epilepsy are still limited, although there are a few perfusion single-photon emission computed tomography (SPECT) studies.[13,14] ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) is a traditional and still useful imaging modality for epilepsy, as it allows measurements of the brain's regional glucose metabolisms with higher resolution than SPECT.[15] ^{18}F-FDG PET is widely utilized to detect the epileptogenic foci as a hypometabolic area.[16]

However, the effect of comorbid psychosis on the brain glucose metabolism in individuals with epilepsy is still unknown. Given the evidence of abnormal ^{18}F-FDG PET findings in schizophrenia,[17,18] we speculated that there may be different patterns of brain metabolism between epilepsy with and without psychosis. We hypothesized that individuals with both psychosis and epilepsy may present different glucose metabolism, for example, greater hypometabolism. We conducted the present study to investigate potential differences in the interictal ^{18}F-FDG PET findings of patients with temporal lobe epilepsy (TLE) with and without interictal psychosis.

Key Points

- Psychosis is an important comorbidity in epilepsy, but its pathophysiology is still unknown.
- We investigated brain metabolisms in temporal lobe epilepsy (TLE) with and without interictal psychosis using ^{18}F-FDG PET.
- Compared to TLE without psychosis, hypermetabolic areas around the upper cerebellum were found in TLE with psychosis.
- These findings may reflect the involvement of the cerebellum in the underlying neurobiology of interictal psychosis.

2 | METHODS

2.1 | Patients

The clinical and imaging data were extracted from our previous study on brain structural networks in 20 patients with TLE with psychosis (TLE-P) and 29 patients with TLE without psychosis (TLE-N).[12] The inclusion and exclusion criteria were described in that paper, and in brief, the diagnosis of TLE was based on the presence of focal seizures consistent with TLE and focal epileptiform discharges in the temporal areas in scalp electroencephalography. Interictal schizophrenia-like psychosis was diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria.[19]

Of these patients, we enrolled 13 consecutive patients with TLE-P and 21 patients with TLE-N who underwent interictal ^{18}F-FDG PET scanning for their intractable seizures and an evaluation of the focus side. The clinical demographics of the enrolled subjects are summarized in Table 1. All of the patients gave written informed consent to have their data examined in this study, which was approved by the Institutional Review Board at National Center of Neurology and Psychiatry, Tokyo Japan.

2.2 | Imaging Acquisition

All 34 patients underwent ^{18}F-FDG-PET using a combined 16-slice PET/CT scanner (Biograph 16; Siemens, Erlangen, Germany). None of the patients had any seizures within the 24 h prior to the examination or during the scan.

After the patients had fasted >6 h, their blood glucose levels were measured before the administration of ^{18}F-FDG, which involved the intravenous injection of

TABLE 1 Demographics of the patients with TLE with and without psychosis

Feature	TLE-N (n = 21)	TLE-P (n = 13)	*P*-value
Men: women	9: 12	6: 7	>0.99[a]
Age at the examination, years, mean ± SD	45.1 ± 11.6	44.7 ± 13.5	0.94[b]
Disease duration, years			
Mean onset age ± SD	15.3 ± 6.8	14.8 ± 16.2	0.91[b]
Mean duration of epilepsy ± SD	29.7 ± 13.1	29.9 ± 14.5	0.97[b]
Clinical features:			
Laterality of focus (L: R)	4:9	11:10	0.38[a]
Patients with HS on MRI	12	6	0.79[a]
No. of ASMs	2.38 ± 0.92	2.23 ± 1.09	0.67[b]
Mean onset age of psychosis ± SD	N/A	31.1 ± 15.5	N/A

Abbreviations: ASMs: anti-seizure medications, HS: hippocampal sclerosis, N/A: not available.
[a]χ^2 test with Yates's correction.
[b]Unpaired *t* test.

4–6 MBq/kg 18F-FDG 40 min before the start of the brain PET/CT scan. For the emission scans (15 min/bed position; matrix 336 × 336; pixel size, 0.89 × 0.89 mm) of the brain PET/CT protocol (one bed position; field of view [FOV] 30.0 cm axial) in 3D mode, a standard PET/CT bed with a built-in head holder was used.

The structural 3D T1-weighted MR images for the spatial normalization process were obtained by the following protocol: repetition time/echo time, 7.18/3.46 ms; flip angle, 10°; effective slice thickness, 0.6 mm with no gap; 300 slices; matrix, 384 × 384; FOV, 26.1 × 26.1 cm.

2.3 | Imaging processing

The interictal ^{18}F-FDG PET images were spatially normalized using the DARTEL (diffeomorphic anatomical registration using the exponentiated lie) method[20] and Statistical Parametric Mapping 12 (SPM12; http://www.fil.ion.ucl.ac.uk/spm/) software running on MATLAB, as in our previous study.[21] Each individual's 3D-T1 image was co-registered and resliced to its ^{18}F-FDG PET image, and then the co-registered 3D-T1 image was normalized with DARTEL. Subsequently, the transformation matrix was applied to the ^{18}F-FDG PET. Finally, the normalized images were smoothed with an 8-mm full-width at half-maximum (FWHM) Gaussian kernel to decrease spatial noise and compensate for the inexactitude of normalization.

To investigate the epilepsy/seizure-related alterations, we performed a focus-side-specific comparison. For our analysis of the left-TLE and right-TLE patients together, PET and MRI images of the left-TLE patients were left-right flipped to make the right hemisphere the ipsilateral hemisphere in both the TLE-P and TLE-N groups before the above-mentioned normalization process, as we did in another study.[22] Since the left/right side might be important for psychiatric disorders, we also performed a group comparison without flipping the images.

2.4 | Statistical analyses

The voxel-wise comparison between TLE-P and TLE-N groups was performed by the "two-sample *t* test" design in the SPM12 program, with age and gender as covariates and the global proportional scaling for PET, which is widely used in ^{18}F-FDG PET studies.[23] To estimate the effect of psychosis, we used the software's "multiple regression" design for a correlation analysis with the duration of psychosis in the TLE-P group with age and gender as covariates and global proportional scaling. Results that met the following criteria were deemed significant: a seed threshold of $P < 0.001$ (uncorrected) and an extent threshold of $P < 0.05$ (family-wise error [FWE]). For the clinical demographic comparison, we used the unpaired *t* test and χ^2 test for continuous and categorical variables, respectively. The pre-study power calculation was performed by G*Power 3.1,[24] which generated approximately 0.60 as the power to detect differences between two groups with 0.80 effect sizes and two-tailed $P < 0.05$.

3 | RESULTS

3.1 | Patient demographics

The clinical demographics of the TLE-P and TLE-N groups are provided in Table 1. There were no significant between-group differences in age, gender, onset/duration of epilepsy, laterality of focus, hippocampal sclerosis, or use of

anti-seizure medications. Of total 34 patients, 17 (8 TLE-P, 9 TLE-N) underwent long-term video-EEG recordings and the ictal EEG showed concordant laterality of focus with interictal EEG and visual ^{18}F-FDG evaluation. The others did not have ictal EEG but the hypometabolic side in ^{18}F-FDG was consistent with interictal epileptiform discharges. Regarding surgical resection, five patients (one TLE-P, four TLE-N) underwent anterior temporal lobe resection, in which almost all patients pathologically showed hippocampal sclerosis except for one TLE-N patient with MRI-negative focal cortical dysplasia and almost all patients had a good seizure outcome, that is, Engel Class I, except for one TLE-N case with hippocampal sclerosis and Engel Class III outcome.

3.2 | PET images

To visually confirm the ^{18}F-FDG hypometabolic areas, we created mean images of each group, after dividing each image by its global mean uptakes. The mean images are shown in Figure 1. Overall, the hypometabolic areas were observed in the ipsilateral temporal pole to hippocampus in both groups (Z = 10, 13, 16).

3.3 | Voxel-wise group comparison

Figure 2 and Table 2 present the results of the group comparisons. We observed significantly increased ^{18}F-FDG signals in the upper cerebellum, superior cerebellar peduncle, and midbrain in the TLE-P group compared to the TLE-N group. The findings were almost the same in the focus-side-specific (Figure 2A) and no-flipping (Figure 2B) analyses. This upper cerebellar hypermetabolism could be visually detectable in the mean images (Figure 1, Z = 19). Since the significant area was the cerebellum, we performed a post hoc analysis with the number of antiseizure medications as an additional covariate. The results were unchanged (Figure S1). In addition, the use of phenytoin did not differ significantly between the patients with and without psychosis: three of the 13 patients in the TLE-P group used phenytoin, as did seven of the 21 patients in the TLE-N group. There were no significant between-group metabolic differences around the focus or other cerebral areas in the focus-side-specific analysis or the no-flipping analysis.

3.4 | Voxel-wise correlation with duration of psychosis

We identified no significant correlative areas at the level of $P < 0.05$ (FWE-correction). At a more lenient threshold, there was a trend-level positive correlation of the ipsilateral posterior fusiform gyrus glycometabolism with the duration of psychosis (uncorrected height $P < 0.001$, cluster $P = 0.032$, Figure S2), although careful interpretation is necessary due to the non-rigorous statistics.

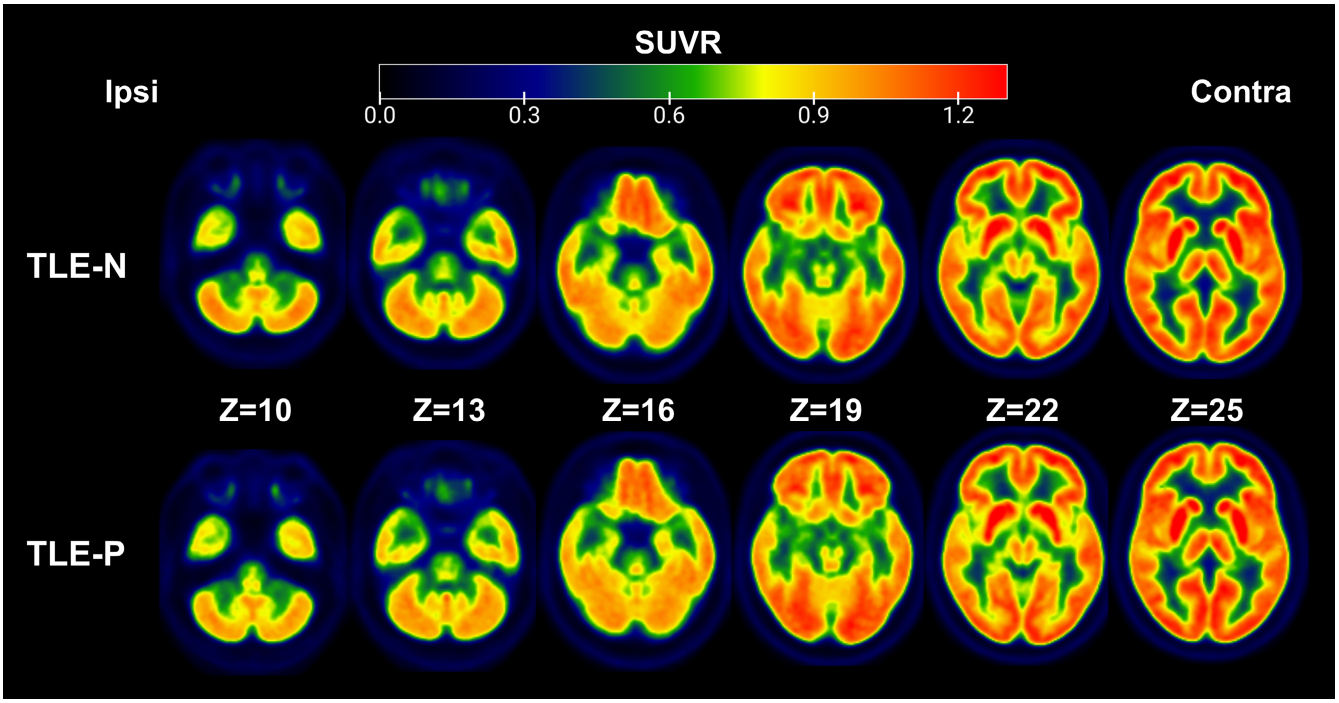

FIGURE 1 The mean standardized uptake value ratio (SUVR) images of the TLE-N (n = 13) and TLE-P (n = 21) groups

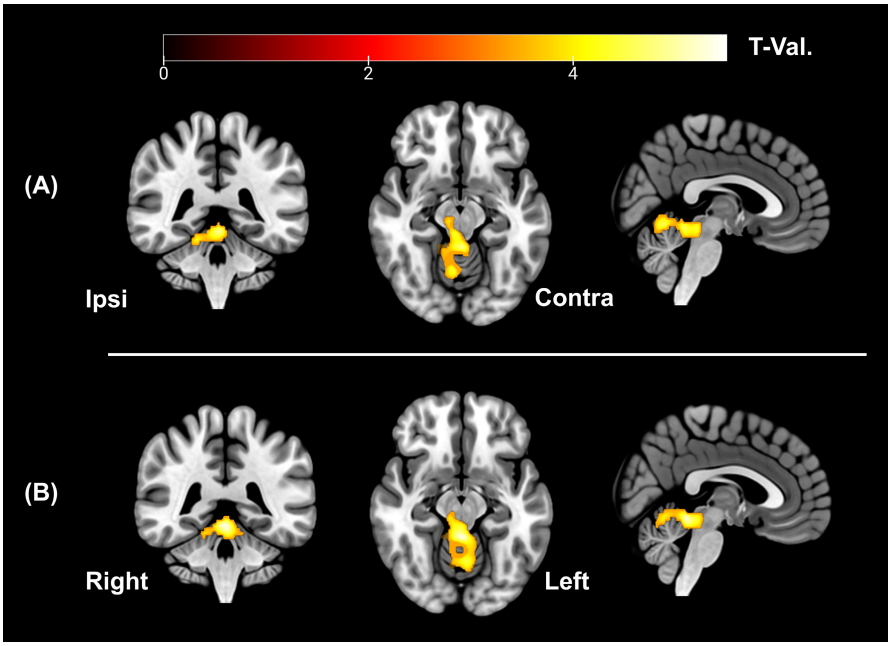

FIGURE 2 The results of the voxel-wise comparison revealed significant glucose metabolism increases in the TLE-P compared to the TLE-N group. The hypermetabolic areas included the upper cerebellum, superior cerebellar peduncle, and midbrain. These findings were consistent in the focus-side-specific (A) and no-flipping (B) analyses.

TABLE 2 Results of voxel-wise analysis by SPM12

	Cluster level			Peak level	MNI Coordinates		
Analysis	**Cluster k**	***P*-value (FWE)**	***P*-value (uncorrected)**	**T-val.**	**X**	**Y**	**Z**
Focus-side specific							
TLE-P > TLE-N	1205	0.005	0.001	5.12	−1	−43	−12
Without L/R flipping							
TLE-P > TLE-N	1586	0.001	0.001	5.48	0	−43	−12

4 | DISCUSSION

We explored the brain metabolic changes in patients with TLE plus interictal psychosis and compared them with the changes in patients with TLE without psychosis. The results of our analyses revealed a significant increase of glucose metabolism in the upper cerebellum to the midbrain in the TLE-P group. To the best of our knowledge, this is the first study to investigate ^{18}F-FDG PET findings in psychosis with epilepsy.

Cerebellar hypermetabolism shown by ^{18}F-FDG PET has been reported in various neuropsychiatric disorders, including traumatic brain injury,[25] dementia with Lewy bodies,[26] alcohol use disorder,[27] and Alzheimer's disease.[28] It has been noted that this finding could be caused in part by the proportional scaling procedure for ^{18}F-FDG PET analysis, but the finding of cerebellar hypermetabolism is currently suspected to play important roles in the metabolic network of the brain.[28] The present study demonstrated that the increased cerebellar metabolic area in the TLE-P group was restricted within the upper areas (Figure 2), which would anatomically correspond to the anterior lobe of the cerebellum.[29] We thus consider that this anatomically consistent result may support the pathophysiological meaning of cerebellar hypermetabolism.

In fact, there has been increasing evidence of cerebellar involvement in neuropsychiatric, emotional, and cognitive dysfunction.[29–32] In terms of the functional topology of the cerebellum, the anterior lobe has conventionally been thought to represent sensorimotor functions, while the posterior lobe is more involved in cognitive function.[32] However, a recent study revealed that expressions of anger and aggression were associated with a more anterior region of the cerebellum,[31] and somatosensory abnormalities have also been reported in psychosis.[33,34] We therefore speculate that our present finding of hypermetabolism in the anterior lobe of the cerebellum may reflect the underlying pathophysiology of interictal psychosis in individuals with TLE.

Two studies have used functional neuroimaging to examine the simultaneous presence of psychosis and epilepsy,[13,14] and interestingly, both studies reported increased cerebral blood flow in patients with TLE with psychosis, in whom the right posterior cingulate gyrus[13]

or right temporal lobe[14] was involved. These studies suggested hyperactivity of the brain in TLE with psychosis, which would support the pathophysiological meaning of cerebellar glucose hypermetabolism. Both studies also described hyperperfusion areas in the limbic system structures. The fusiform gyrus, where we detected a trend-level positive correlation with the duration of psychosis, is adjacent to the hippocampus or parahippocampal gyrus. It is possible that in individuals with both psychosis and epilepsy, such (para-) limbic activities could be increased over time, and the increased activity might be associated with the underlying mechanisms of psychosis in epilepsy.

In addition to these functional studies, most structural neuroimaging studies reported cerebral abnormalities in patients with epilepsy of psychosis[8–12]; we observed no significant difference in the cerebrum between the present TLE-P and TLE-N groups. This unexpected discrepancy might be caused by the small sample size in this study. In addition, the ipsilateral hypometabolic areas are usually widespread beyond the focus temporal lobe in TLE itself,[15] and it might have been difficult to detect the effect of psychosis on such already decreased cerebral metabolisms.

According to a previous study investigating ^{18}F-FDG PET between TLE and healthy subjects, patients with TLE presented reduced metabolisms in ipsilateral mesial and lateral temporal lobe and a part of frontal lobe, as well as mesiotemporal hypermetabolism on the contralateral side.[35] Thus, as the abnormal brain glucose metabolism in TLE can be found mainly around temporal lobe compared with healthy controls, we may speculate that both TLE with and without psychosis could show similar abnormalities and the upper cerebellar findings would be a characteristic feature of TLE with psychosis, despite the lack of healthy data in our study.

The reported findings of brain glucose metabolism in schizophrenia have been relatively diverse.[17,18,36–39] Notably, hypermetabolic patterns in schizophrenia were frequently described,[17,36,39] while reduction was also sometimes observed.[37] The commonly reported hypermetabolic areas are the frontal lobe[36,39] and white matter.[17] Thus, although brain glucose hypermetabolism might be a common finding between schizophrenia and psychosis of epilepsy, the precise mechanisms seem to be different. Further investigations including patients with schizophrenia and healthy controls are necessary to clarify this point.

This study has several limitations. First, the sample size was small (n = 13 TLE-P, n = 21 TLE-N), which makes the present findings somewhat preliminary. However, this is the first ^{18}F-FDG PET study of the brain metabolism of patients with both psychosis and epilepsy, and the results of the group comparison were relatively robust statistically (cluster $P < 0.005$, FWE-corrected, Table 2). On the other hand, considering the result of power calculation, there remains a possibility to have overlooked small or medium size of other differences. Second, due to the lack of healthy controls, we could not investigate the range of abnormalities in each group compared to the healthy brain. A comparison with patients with schizophrenia is also desirable to further examine specific patterns in psychosis of epilepsy. Our choice of reference area for the ^{18}F-FDG PET analysis might also be controversial, but global proportional scaling is a widely used method, and there is no established specific reference brain region for individuals with TLE with and without psychosis. It was reported that hypermetabolic findings derived from the global proportional scaling method have an important pathological meaning.[28] Another limitation was the lack of detailed clinical data. Information of the dominant hemisphere and handedness was not available, although the result of cerebellar hypermetabolism was symmetric. Laterality of focus was evaluated by ictal EEG recording in only a half of patients, while ^{18}F-FDG PET also have 85%-90% sensitivity for lateralization of TLE focus.[15] Detailed focus localization, for example, mesial or lateral temporal lobe, was lacking except for patients with surgical outcome or hippocampal sclerosis, and history of febrile status epileptic was also unknown. Moreover, the possible effect of psychiatric drugs, particularly antipsychotics, was not evaluated. Although we performed an additional analysis with the number of ASMs as a covariate, the effect of medications could still be a potential confounder, especially for the symmetric findings. These limitations should be noted for careful interpretation.

In conclusion, this ^{18}F-FDG PET study demonstrated significant glucose hypermetabolism in the upper cerebellum in patients with both TLE and interictal psychosis compared to patients with TLE without psychosis. These findings may reflect the involvement of the cerebellum in the neurobiological mechanisms of interictal psychosis and could contribute to a better understanding of this disorder.

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CONFLICTS OF INTEREST

None of the authors has any conflict of interest to disclose.

ETHICS STATEMENT

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with the guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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