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Because the human brain consumes a disproportionate fraction of the resting body’s energy, positron emission tomography (PET) measurements of absolute glucose metabolism (CMRglc) can serve as disease biomarkers. Global mean normalization (GMN) of PET data reveals disease-based differences from healthy individuals as fractional changes across regions relative to a global mean. To assess the impact of GMN applied to metabolic data, we compared CMRglc with and without GMN in healthy awake volunteers with eyes closed (i.e., control) against specific physiological/clinical states, including healthy/awake with eyes open, healthy/awake but congenitally blind, healthy/sedated with anesthetics, and patients with disorders of consciousness. Without GMN, global CMRglc alterations compared to control were detected in all conditions except in congenitally blind where regional CMRglc variations were detected in the visual cortex. However, GMN introduced regional and bidirectional CMRglc changes at smaller fractions of the quantitative delocalized changes. While global information was lost with GMN, the quantitative approach (i.e., a validated method for quantitative baseline metabolic activity without GMN) not only preserved global CMRglc changes but also detected regional CMRglc variations in the congenitally blind. These results caution the use of GMN upon PET-measured CMRglc data in health and disease.

1. Introduction

Noninvasive neuroimaging with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) provide the foundations of human brain mapping, as practiced in the past four decades for PET and three decades for fMRI [1–4]. Early PET studies concentrated on quantitative imaging of resting-state blood flow and metabolism [2, 5], whereas later PET and then fMRI studies used tools with some form of global mean normalization.
(GMN), most notably statistical parametric mapping (SPM), or the Scaled Subprofile Model of principal component analysis (SSM-PCA), to obtain regional differences among control and metabolically/functionally perturbed states. When these methods are applied to PET metabolic radiotracers, such as $^{18}$Ffluorodeoxyglucose (FDG), the application of these analysis tools often proceeded with the assumption that global brain metabolic activity, defined as the mean metabolic rate of gray matter or the entire brain, is a valid basis for normalization of regional values, in part because it is held to facilitate group comparisons in the presence of physiological and/or experimental intraindividual and interindividual differences [6, 7]. GMN yields parametric images of fractional or percentage differences from a variably defined global mean. While it is not a formal requirement for either SPM or SSM-PCA, GMN has become an almost routine method to facilitate group comparisons in the presence of physiological rate of gray matter or the entire brain, is a valid basis for normalization of regional values, in part because it is held to facilitate group comparisons in the presence of physiological and/or experimental intraindividual and interindividual differences [6, 7]. GMN yields parametric images of fractional or percentage differences from a variably defined global mean. While it is not a formal requirement for either SPM or SSM-PCA, GMN has become an almost routine method to facilitate group comparisons in the presence of physiological rate of gray matter or the entire brain, is a valid basis for normalization of regional values, in part because it is held to facilitate group comparisons in the presence of physiological and/or experimental intraindividual and interindividual differences [6, 7].

GMN obscures evidence of metabolic changes in the brain among the regional CMR$_{glc}$ of a group of subjects or across different metabolic states, with subsequent application of network analysis to the regions that differ among groups and/or conditions [19]. Most resting-state fMRI and PET studies thus use some form of GMN prior to comparison of the data for network determination. However, our focus here is only the effects of GMN upon PET imaging.

The validity of the GMN procedure for creating metabolic maps originally remained uncontested on the assumption that most glucose and oxygen consumed in the resting-state served "nonfunctional" mechanisms which are uncorrelated with cognitive activity [20]. However, results from both early and more recent studies challenge this assumption [18, 21]. The resting brain is the most energy-demanding organ in the human body [22], the energy turnover due to Na$^+$,K$^+$-ATPase function that sustains membrane repolarization and ion gradient restoration for continuous neuronal activity [23–25]. It is well accepted that energy demands of neuronal activity in the resting awake human brain by far exceed the magnitude of the additional energy turnover associated with evoked or spontaneous changes of functional activity [26]. Yet, the fraction of the total metabolic rate altered by spontaneous or evoked events remains uncertain, and the extent to which GMN obscures differences of the energy demand across functional states thus still remains uncertain. In this context, CBF and CMR$_{O2}$ values measured in healthy aging and in Parkinson’s disease show that conventional GMN obscures evidence of metabolic changes in the brain [27, 28]. Borghammer et al. showed that GMN of quantitative PET-measured CBF measurements can yield false positive findings of perfusion changes [10], but the methods are nonetheless being generalized to metabolic PET scans [29]. Borghammer et al. also demonstrated that foci of elevated CBF attributed to small brain regions actually can arise as a consequence of normalization applied only to gray matter [11]. In an examination of simulated reduction of cortical metabolism, Borghammer et al. further noted that GMN generally only recovered a few percent of the original signal and conversely led to artificial findings of relative increases [12]. Thus, there are two issues that potentially affect the use of PET images as biomarkers of disease; the raising of regional differences to significance and the removal of global differences among individuals and groups that results from GMN.

Prompted by this evidence, we sought to test the hypothesis that GMN may not only artificially raise minor regional variations to significance but also may significantly obscure global metabolic effects when PET images of the resting brain in specific disorders are compared. We used FDG-PET to measure CMR$_{glc}$ at different sites, where the control states
(of resting healthy awake volunteers with eyes closed) were compared to subjects in states established by conditions ranging from normal sensory input to sedation by anesthesia to different clinical states. While some experiments involved blood sampling of the FDG tracer’s supply to the brain, necessary to obtain absolute values of CMR$_{\text{glc}}$ (aCMR$_{\text{glc}}$), others did not. To compare FDG-PET images from different sites, we developed a new method allowing quantitative measures of CMR$_{\text{glc}}$ (qCMR$_{\text{glc}}$) by a calibration procedure that is based on comparison of qCMR$_{\text{glc}}$ data with aCMR$_{\text{glc}}$ data for a control state (i.e., healthy awake with eyes closed). We then validated the method, which is aimed for quantitative baseline metabolic activity without GMN, by first comparing qCMR$_{\text{glc}}$ values found in control experiments from different sites and then comparing qCMR$_{\text{glc}}$ to aCMR$_{\text{glc}}$ for experiments with blood sampling. We tested conditions that included awake and eyes open states (presence of sensory input), pharmacological intervention (anesthesia), disorders of consciousness, and congenital blindness (clinical states), in comparison to resting healthy awake subjects with eyes closed (control). Comparison of t-maps of CMR$_{\text{glc}}$ without GMN reveal heuristically important and pathognomonic evidence of perturbations of brain metabolism across states or among groups. However, GMN induced artificial relative increases in states that are generally accepted as only inducing metabolic decreases.

2. Materials and Methods

2.1. Subjects. Participants underwent tomography at four sites, and imaging at each site included a control group. FDG-PET measures were collected in a total of nine different resting states (Table 1) and compiled as anonymized data, most of which previously had been published prior to the present analysis. A group of healthy awake subjects imaged with eyes closed (HAEC) was recorded at each site. Each site’s HAEC served as control for the other groups recorded at that site. There were 8 other groups: healthy awake subjects with eyes open (HAEO) [30]; healthy subjects sedated with 1% desflurane (Des1%), 0.25% sevoflurane (Sev0.25%) [31], or 0.5% sevoflurane (Sev0.5%); awake congenitally blind (CB) subjects [32]; and patients with disorders of consciousness, including unresponsive wakefulness syndrome (UWS), minimally conscious state (MCS), and emergence from MCS (EMCS) [33]. The diagnostic criteria for the selected disorders of consciousness have been described earlier [34]. All healthy participants were right-handed.

Among the five groups of healthy volunteers, two without sedation (HAEC and HAE0) underwent tomography in Munich, Germany, and those with sedation (Sev0.25%, Sev0.5%, and Des1%) in Irvine, CA, USA. Among the four groups with some form of disability, the CB underwent tomography in Copenhagen, Denmark. All three groups with disorders of consciousness had tomography in Liège, Belgium. All tomograms were acquired upon obtaining written informed consent from participants or from caregivers (in the case of disorders of consciousness), in accordance with the Helsinki Protocol, and all studies were approved by the appropriate ethical review board per institution; the Ethics Committee of the University Hospital of Liège (Belgium), the Research Ethics Committee of the University of Copenhagen and Frederiksberg (Denmark); the Institutional Review Board at the University of California, Irvine (USA); and the ethics review board of the Klinikum Rechts der Isar, Technische Universität München (Germany).

2.2. Tomography. All subjects underwent FDG-PET and MRI scanning. Details of FDG-PET and MRI acquisition are described in the original studies [30–34]. Briefly, tomographies in USA and Denmark were performed on Siemens ECAT high-resolution research tomographs (HRRT), in Germany on a Siemens Biograph mMR PET/MRI, and in Belgium on a Philips GEMINI TF PET/CT. Blood sampling in USA subjects allowed calculation of absolute values of CMR$_{\text{glc}}$ (aCMR$_{\text{glc}}$) [31].

2.2.1. Tomography (Site Number 1). The two healthy groups without any sedation, consisting of 11 HAEO subjects (aged 52 ± 10 years, 7 males) and 11 different HAE0 subject (aged 57 ± 10 years, 8 males; i.e., HAE0GER), all used an MRI/PET tomograph (Siemens Biograph mMR) at the Neuroimaging Center of Technical University of Munich, Germany (Table 1). Subjects held their eyes closed or open depending on their assigned group; details of the scans have been published elsewhere [30]. Structural MRI data were acquired (magnetization-prepared 180-degree radiofrequency pulses and rapid gradient-echo (MP-RAGE), repetition time (TR) 2.3 s, echo time (TE) 2.98 ms, 160 slices with 0.5 mm gap, 256 × 256 mm field of view (FOV), 256 × 256 matrix size, and 5 minutes and 3 seconds). About 30 minutes after the bolus FDG injection, a 10-minute emission recording was acquired (saturated list mode, 128 slices with 0.5 mm gap, 192 × 192 mm matrix, and 3.7 × 2.3 × 2.7 mm voxel).

2.2.2. Tomography (Site Number 2). The three sedated groups (age range 18–22 years), consisting of 8 Sev0.25% subjects, 8 Sev0.5% subjects (same cases as Sev0.25%), and 7 Des1% subjects, were all scanned using the Siemens ECAT high-resolution research tomograph (HRRT) at the Department of Anesthesiology of the University of California, Irvine, California, USA, and also underwent MRI (Table 1). Details of the tomographies of the Sev0.25% group, same as the other groups, have been published elsewhere [31]. Two intravenous catheters were inserted, one for arterial venous blood sampling and the other for FDG infusion (203.5 MBq) enabling measurement of absolute CMR$_{\text{glc}}$. A brief attenuation scan was obtained using a Cs-137 source, and a ten-minute emission recording was obtained (207 slices at 1.2 mm gap) beginning 32 min after FDG application; participants were still for the tracer uptake interval, except when asked to perform a hand gesture as a test of alertness/sedation. The tomograph had an effective resolution of 3.3 mm full width at half maximum (FWHM). Participants had tomographies on different occasions for the selected doses of anesthetic gases, delivered with standard calibrated vaporizers in 100% oxygen via a standard semicircle breathing circuit using a Dräger AV anesthesia machine. A Datex Ohmeda Capnomac Ultima (Helsinki, Finland) was...
used to monitor expired CO₂ and anesthetic gas levels. This HAEC group consisted of the participants who received 0% sevoflurane (HAEC-sev; n = 8; Table 1) and 0% desflurane (HAEC-des; n = 7; Table 1).

2.2.3. Tomography (Site Number 3). PET data were acquired in a group of 7 CB participants (three males aged 41 ± 8 years) and 7 HEAC (aged 25 ± 5 years, four males; HAECDEN) using a Siemens ECAT HRRT at Rigshospitalet in Copenhagen, Denmark (Table 1). Participants’ MRIs were acquired using a 3 T Siemens Trio MRI scanner at the Danish Research Centre for Magnetic Resonance, Hvidovre Hospital, Hvidovre, Denmark. Details of the scans have been published elsewhere [32]. One among the seven CB participants had limited vision at birth that progressed to complete blindness at the age of seven; all others were completely blind from birth. Structural MRI data were acquired (MP-RAGE, TR 1.5 s, TE 3.93 ms, inversion recovery time (TI) 0.8 s, 256 slices with no gap, 192 × 256 mm FOV, and 6 minutes 36 seconds). PET data were acquired forty minutes after bolus injection of approximately 210 MBq FDG (single frame, OSEM3D mode, 207 slices with no gap, 1.2 × 1.2 × 1.2 mm voxels, and 40 minutes). During the tracer uptake period, control participants were blindfolded and all participants rested in a dimly lit room without falling asleep.

2.2.4. Tomography (Site Number 4). The groups with disorders of consciousness consisted of (i) 49 UWS patients (aged 46 ± 16, 31 males; mean time since injury 1.7 ± 3.2 years), (ii) 65 MCS patients (aged 40 ± 16, 41 males; mean time since injury 3.3 ± 4.3 years), and (iii) 17 EMCS patients (aged 35 ± 15, 15 males; mean time since injury 3.0 ± 3.7 years). The control group (HAECBEL) consisted of 28 participants (aged 44 ± 16, 16 males). All participants were scanned using the Philips GEMINI TF PET/CT device at the University Hospital of Liege, Liege, Belgium (Table 1), according to procedures described in detail elsewhere [33–35]. About 30 min after intravenous FDG injection, a single 12-minute emission frame was recorded (90 slices with no gap, 256 × 256 matrix, and 2 × 2 × 2 mm voxels). The control subjects were kept awake in a dimly lit room during the FDG uptake, and all patients were kept awake during FDG uptake.

2.3. Registration. All PET images were registered to the Montreal Neurological Institute (MNI) space (3 × 3 × 3 mm) using a combination of linear and nonlinear registration tools on publicly available platforms (i.e., advanced normalization tools (ANTs) from http://stnava.github.io/ANTs, or BioImage Suite from http://bioimagesuite.yale.edu). PET images from Germany, USA, and Denmark were first registered to their corresponding MRI image using a rigid body transformation and then carried to the MNI template by computed affine and nonlinear transformations, with interpolation to a 3 × 3 × 3 mm³ voxel size. Belgian PET images were directly registered to a common PET template created from the HAECDEN group, using a combination of linear and nonlinear registrations applying very restrictive and highly regularized registration parameters.

2.4. Calibrating Quantified Measures of CMRglc (qCMRglc). As shown in Table 1, only the USA site had blood sampling data to enable FDG-PET counts to be converted into “absolute CMRglc” units of μmol/g/min (aCMRglc). To compare metabolic measurements recorded from different sites (where blood sampling data were unavailable), we developed a new method for calibrating quantified measures of CMRglc (qCMRglc) that targets quantitative baseline metabolic activity without GMN. This method is based on the comparison of qCMRglc data with aCMRglc data also for the HAEC condition from Hyder et al. study (aCMRglc-HYD), with a mean male age of 26.1 ± 3.8 years [36]. For consistency of the data from the USA site with data from other sites, we also calculated qCMRglc for these five USA datasets, which in turn provided the validation for our procedure (see below).

Our goal was to preserve between-state global differences in metabolism, which are believed to be removed by GMN. Previous work has demonstrated that for identical conditions (i.e., HAEC), region-to-region aCMRglc variation is proportional to region-to-region PET radiation counts [37]. We opted to apply per-site fitting procedure by using the same

<table>
<thead>
<tr>
<th>PET imaging site</th>
<th>Experimental group</th>
<th>Control group</th>
</tr>
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<tbody>
<tr>
<td>Site number 1, Germany (Technical University of Munich)</td>
<td>HAEO (n = 11)</td>
<td>HAECDEN (n = 11)</td>
</tr>
<tr>
<td>Site number 2, USA (University of California, Irvine)</td>
<td>° Sev0.25% (n = 8)</td>
<td>° HAEC serviced (n = 8)</td>
</tr>
<tr>
<td>Site number 3, Denmark (Rigshospitalet, Copenhagen University Hospital)</td>
<td>° Des1% (n = 7)</td>
<td>° HAEC serviced (n = 7)</td>
</tr>
<tr>
<td>Site number 4, Belgium (University Hospital of Liege)</td>
<td>UWS (n = 65)</td>
<td>MCS (n = 65)</td>
</tr>
<tr>
<td></td>
<td>EMCS (n = 17)</td>
<td>HAECDEN (n = 7)</td>
</tr>
</tbody>
</table>
| ° indicates that both absolute CMRglc (aCMRglc) and quantified CMRglc (qCMRglc) were obtained from the USA site, enabling comparison between them (see Figures 1(b) and 1(c)). aCMRglc: absolute CMRglc with blood sampling of the tracer FDG supply to the brain; qCMRglc: calibration of quantified comparing qCMRglc with aCMRglc for HAEC only eqs. (1 and 2); HAEC: healthy people awake with eyes closed (control condition); HAECDEN: healthy people awake with eyes open; Des1%: healthy people sedated with 1% desflurane; Sev0.25%: healthy people sedated with 0.25% sevoflurane; Sev0.50%: healthy people sedated with 0.5% sevoflurane; CB: awake people with congenital blindness; UWS: patients who were unresponsive wakefulness syndrome; MCS: patients who were in a minimally conscious state; EMCS: patients who emerged from MCS.
linear model for all individuals at a given site. Assuming HAE groups are comparable across sites [19], then this procedure would have the potential to compare metabolic differences between states recorded at different sites.

The “quantified CMRGlc” metric, referred to as qCMRGlc to focus on quantitative baseline metabolic activity without GMN, was obtained in two steps. First, a linear intensity transformation of the original tissue radioactivity values was computed on a per-site basis, such that the distribution of voxels in the mean across the gray and white matter of the cerebrum (excluding the cerebellum) from each site was matched in intensity to the distribution of voxels from the published aCMRGlc-HYD database [36]. The similarity between the distributions was calculated as the Jensen-Shannon Divergence [38] (JSD), where the per-site linear intensity transformation was calculated as the minimization of the following expression:

\[
\text{JSD} \left\{ \text{dist} \left( \text{aCMRGlc - HYD} \right) - \text{dist} \left( \text{a}_{\text{site}} \cdot \text{FDG}_{\text{HAEC}} + b_{\text{site}} \right) \right\},
\]

where \text{dist} \left( \text{aCMRGlc - HYD} \right) and \text{dist} \left( \text{aCMRGlc-HAEC} \right), respectively, refer to the distribution of voxels in the mean across the gray and white matter of the cerebrum (excluding the cerebellum) of the published aCMRGlc-HYD database [36] and the original tissue-radioactivity values for each HAE group (FDGHAEC) from any site (Table 1), and \text{a}_{\text{site}} and \text{b}_{\text{site}} are, respectively, the resultant slope and intercept from the fit, unique for the specific site. Prior to minimization of eq. (1), \text{FDG}_{\text{HAEC}} was spatially smoothed to match the point-spread function of \text{aCMRGlc-HYD} as computed by the 3dFWHMx program from the AFNI software package. Then, the qCMRGlc maps for each subject were computed by applying the \text{a}_{\text{site}} and \text{b}_{\text{site}} from eq. (1) as follows:

\[
\text{qCMRGlc} = a_{\text{site}} \cdot \text{FDG} + b_{\text{site}},
\]

where FDG refers to tissue-radioactivity concentrations from any individual voxel for any single subject in any group and only for the specific site for which \text{a}_{\text{site}} and \text{b}_{\text{site}} were calculated. The calculated qCMRGlc was used throughout this study as fitted between each site’s HAE group and all other groups from that site. The qCMRGlc calculation was carried out using the distributions of only intracranial voxels.

Two tests were run to validate qCMRGlc. First, if comparable qCMRGlc values exist in HAE groups from different sites, this would indicate that between-site comparisons are possible. To test this, the mean qCMRGlc within 41 gray matter regions (Table S1) drawn in the MNI reference space was calculated for the five control groups (HAEDES, HAECEGEN, HAECEGEN, HAECEDES and HAECEBR) and aCMRGlc-HYD from Hyder et al. [36] that also represented the HAE condition. Pearson correlation and Euclidean distance were calculated between the group means of aCMRGlc-HYD and qCMRGlc in their respective 41 gray matter regions repeated for each pair of groups. Then, \rho values for statistical significance were calculated with permutation testing across the 41 gray matter regions with 1000 repetitions and rerunning the correlation and distance calculations then taking the percentile of the actual correlation/distance based on the randomly permuted correlations/distances as a null distribution (one-sided test, Pearson correlation higher than the null hypothesis and Euclidean distance lower than the null hypothesis).

Second, as a further test of the ability to compare qCMRGlc between groups, we used aCMRGlc data that was available from the USA site. The Des1% and HAECEDES groups had the same subjects, as did the Sev0.25%, Sev0.5%, and HAECESEV groups. The same data were also used to calculate qCMRGlc (see above). Means of aCMRGlc and qCMRGlc were calculated within each gray matter region across all subjects. Treating the respective HAE group as the x-axis and the respective anesthetized group as the y-axis, a linear fit was calculated. The slopes from the linear fits from aCMRGlc were compared to those from qCMRGlc to establish the validity of our calibration method.

2.5. Image Analysis. Mean qCMRGlc maps were computed as the voxel-by-voxel average across each group of subjects and for the combined group of control subjects from all tomography sites. Statistical t-maps were computed using an unpaired voxel-wise two-sample two-tailed Student’s t-test, assuming equal variance for qCMRGlc images following smoothing with an 8 mm Gaussian kernel. Statistical t-maps were also generated with the same parameters following GMN images, with individual scaling to the whole-brain mean of qCMRGlc. Statistics were computed both for qCMRGlc and GMN images using the gray matter regions (Table S1) for difference of each state from the HAE condition.

3. Results

3.1. Validating Quantified Measures of CMRGlc (qCMRGlc). We compared the mean quantified estimates of CMRGlc (qCMRGlc) across 41 gray matter regions for the five HAE groups listed in Table 1 to absolute CMRGlc (aCMRGlc) of the HAE group from Hyder et al. [36] (aCMRGlc-HYD), as shown in Figure 1(a). The Pearson correlation and Euclidean distance between each pair of groups are listed in Table 2. All correlations were highly significant, and Euclidean distances were less than half of the mean in even one dimension, despite there being 41 dimensions. Although HAECESEV and HAECEDES correlated the highest because the subjects in these groups overlapped, different groups of subjects (e.g., HAECEDES and HAECEDEN or HAECESEV and HAECEDEN) had similarly high correlation. We attribute the high correlation among control subjects to the tight age group. The \rho values resulting from comparing actual correlations and distances to an artificially generated null distribution were zero (for Pearson correlation, the value is higher than for 1000 random permutations; for Euclidean distance, the value is lower than for 1000 random permutations). The values indicate that all HAE groups, whether associated with aCMRGlc or qCMRGlc, were highly similar in terms of both spatial extent (correlation) and actual value (distance), confirming that it is valid to compare the HAE groups from different sites.

Figure 1(b) shows the linear fit between the states of anesthesia and respective control states using the aCMRGlc.
estimates from site number 2, while Figure 1(c) shows the same fit for qCMR\(_{\text{glc}}\) estimates where a slope of less than 1 in both Figures 1(b) and 1(c) corresponds to a lower qCMR\(_{\text{glc}}\) in the anesthetized group compared to the control group. All linear fits had \(R^2 \geq 0.95\). The slopes of the linear fits were nearly identical for aCMR\(_{\text{glc}}\) and qCMR\(_{\text{glc}}\) (Des1\%: 0.69 versus 0.68; Sev0.25\%: 0.86 versus 0.84; and Sev0.5\%: 0.79 versus 0.78). We also noted small but consistent shifts of intercepts between the healthy awake and sedated, which were reproducible for aCMR\(_{\text{glc}}\) and qCMR\(_{\text{glc}}\) (Des1\%: 0.045

Figure 1: Validation of quantified CMR\(_{\text{glc}}\) (qCMR\(_{\text{glc}}\)). (a) Comparison of absolute CMR\(_{\text{glc}}\) from Hyder et al. [36] (aCMR\(_{\text{glc}}\)-HYD) with qCMR\(_{\text{glc}}\) from five sites for the HAEC condition (Table 1). Bars represent the mean across all subjects in each group for gray matter regions (Table S1), where error bars are one standard deviation. All qCMR\(_{\text{glc}}\) and aCMR\(_{\text{glc}}\)-HYD values were very similar both relatively between regions and in terms of mean value, suggesting across-site comparisons are possible with our procedure for quantified CMR\(_{\text{glc}}\). The Pearson correlation and the Euclidean distance (Table 2) suggest high similarity and low difference of CMR\(_{\text{glc}}\) for the HAEC group across all sites. (b) Scatter plots, from left to right, for aCMR\(_{\text{glc}}\) between Des1\%, Sev0.25\%, or Sev0.5\% groups and equivalent HAEC groups (Table 1). Each point is one gray matter region (Table S1). Slope and \(R^2\) from a linear fit are shown, and units are \(\mu\text{mol/g/min}\), where a slope of less than 1 corresponds to a lower CMR\(_{\text{glc}}\) in the anesthetized group compared to the control. (c) Same as in (b), except using qCMR\(_{\text{glc}}\) from each group. The slopes are almost identical in (b) and (c), indicating that the calculation of qCMR\(_{\text{glc}}\) does not alter the relationship between groups for aCMR\(_{\text{glc}}\).
Table 2: Results of quantified CMRglc (qCMR glc) from Figure 1(a), where HAEC groups from different sites are compared to absolute CMRglc from Hyder et al. [36] (aCMRglc-HYD). The upper triangular half is Pearson correlation (italicized), whereas the lower triangular half is Euclidean distance (non-italicized). In the table \( p = 0 \) for all entries. The Pearson correlations were highly significant, and all the Euclidean distances were less than even one despite a total of 41 dimensions’ means. The high similarity between qCMR glc in the HAEC groups measured at different sites indicates that comparisons between sites are possible using our procedure for quantified CMRglc.

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versus 0.062; Sev0.25%: 0.013 versus 0.024; and Sev0.5%: 0.011 versus 0.024). The largely consistent slope estimates for aCMRglc and qCMRglc in Figures 1(b) and 1(c) demonstrate that group-to-group differences present in aCMRglc estimates were preserved after calculating qCMR glc.  

#### 3.2. qCMR glc across Different States

Compared to the eyes closed condition of the HAEC control group members (0.31 ± 0.06 μmol/g/min), the eyes open HAEO group members had higher global estimates of qCMR glc (0.34 ± 0.06 μmol/g/min) and the CB members had similar global gray matter estimates of qCMR glc (0.31 ± 0.05 μmol/g/min), as shown in Figure 2(a). The HAEO group members had 8–12% higher global qCMR glc estimates (0.34 ± 0.06 μmol/g/min) compared to the members of the HAEC control group in both gray and white matter regions (Figures S1A and S2A, resp.). The qCMR glc differences between HAEC and HAEO match reports of simple radiation counts [37]. In contrast, members of the CB group revealed only insignificant differences of global qCMR glc estimates across gray and white matter regions, compared with members of the HAEC groups (Figures S1B and S2B, resp.). Table 3 shows the relationship of qCMR glc when comparing different states to the control condition as assessed by linear regression analysis with intercept at zero (intercept = 0) and a floating intercept (intercept ≠ 0). Compared to HAEC, decreasing slopes were observed from HAEO to CB to Sev0.25% to Sev0.5% to Des1% to EMCS to MCS to UWS in both gray and white matter, and this pattern did not change with the regression method. There were minimal differences in the slopes (less than 16%) between the two regression methods except for UWS, which also had the largest intercept (0.07 in gray matter and 0.05 in white matter). The intercepts in all other states were much smaller in comparison, suggesting that intercept at zero is a sufficient approximation for most of the states examined (Figures S1 and S2).

Compared to HAECE controls, the groups of individuals under sedation (Sev0.25%, Sev0.5%, and Des1%) had lower global qCMR glc estimates (0.29 ± 0.06, 0.27 ± 0.05, and 0.27 ± 0.05 μmol/g/min in gray matter, respectively; Figure 2(b)). Compared to the HAEC control group members, members of the three sedation groups had 8–15% lower qCMR glc estimates in gray matter (Figure S1C) and 8–12% lower estimates in white matter (Figure S2C).

Compared to the HAEC group of control subjects, patients with disorders of consciousness (UWS, MCS, and EMCS) all had significantly lower qCMR glc estimates (0.20 ± 0.04, 0.19 ± 0.04, and 0.14 ± 0.02 μmol/g/min in gray matter, resp.; Figure 2(c)). Compared to the HAEC control group, the clinical states had 36–54% lower estimates of qCMR glc in gray matter (Figure S1D) and 29–43% lower estimates in white matter (Figure S2D).

#### 3.3. Statistical t-Maps for qCMR glc and GMN Data across States

Relative to the HAEC control group, the statistical t-maps for the disorders of consciousness groups (UWS, MCS, and EMCS) all had significantly lower qCMR glc estimates, whereas other regions had relative hypometabolism (Figure 3(b)). Compared to the MCS and EMCS group members, the UWS group had areas of relative hypermetabolism in subcortical gray matter (Figure 3(b)).

The Sev0.25%, Sev0.5%, and Des1% groups all showed global metabolic decrease in the qCMR glc t-maps (Figure 4(a)), with the Des1% group having less of a decline in white matter than the Sev0.25% and Sev0.5% groups. In contrast, using GMN t-maps, the Sev0.25%, Sev0.5%, and Des1% groups all had a regional pattern of both hypometabolism and hypermetabolism (Figure 4(b)). The Des1% group had relative hypermetabolism of deep brain regions, whereas the Sev0.25% and Sev0.5% groups had common patterns of bidirectional change that were most pronounced and of greatest spatial extent in the Sev0.5% group.

The HAEC group had diffuse global increases, estimated from the qCMR glc t-maps with the greatest increase in the occipital cortex (Figure 5(a)), while GMN t-maps in contrast showed relative white matter hypermetabolism and gray...
matter hypometabolism, except in the visual cortex, which had hypermetabolism (Figure 5(b)). Only the CB group members had brain regions of both metabolic increases and decreases (albeit of smaller magnitudes) in the qCMR$_{glc}$-maps, with the increases mainly in the visual cortex and the decreases beyond the visual cortex (Figure 6(a)). This pattern was repeated when the GMN t-maps revealed large domains of hypometabolic and hypermetabolic cortices, with vision areas showing the strongest relative hypermetabolism (Figure 6(b)). While in the qCMR$_{glc}$-maps the hypometabolic (green in Figure 6(a)) and hypermetabolic (red in Figure 6(a)) regions revealed homogenous activities, in the GMN t-maps the hypometabolic (blue and green in Figure 6(b)) and hypermetabolic (red and yellow in Figure 6(b)) regions showed heterogeneous activities.

The hot and cold colors in Figures 3–6 enabled visualization of the effect upon thresholding. However, we could not apply the same statistical threshold across all conditions because of large variation of groups’ sizes (Table 1). Thus, we used thresholding as a means to reveal positive and negative clusters with GMN versus qCMR$_{glc}$ images, when compared to the control condition of eyes closed (Table 4). With disorders of consciousness (Figure S3), for the qCMR$_{glc}$ images there were only large-sized negative clusters (>98% of voxels), whereas in GMN images there were many smaller-sized negative (6–7% of voxels) and positive (0.1–14% of voxels) clusters. With anesthesia sedation (Figure S4), for the...
qCMR\textsubscript{glc} images there were only large-sized negative clusters (71–96% of voxels), whereas in GMN images there were many smaller-sized negative (0.2–13% of voxels) and positive (0.3–11% of voxels) clusters. With eyes open in awake/healthy (Figure S5), for the qCMR\textsubscript{glc} images there was only one large-sized positive cluster (60% of voxels), whereas in GMN images there were many smaller-sized negative (2–20% of voxels) and positive (0.1–9% of voxels) clusters. With congenitally blind (Figure S6), for the qCMR\textsubscript{glc} images there was only one small-sized positive cluster and two small-sized negative clusters (each 1% of voxels), whereas in GMN images there was one large-sized negative cluster (45% of voxels) and three smaller-sized positive clusters (0.2–27% of voxels) clusters. In brief, the thresholded \textit{t}-maps showed that the number of positive/negative clusters in the GMN images were much greater (Table 4). Thus, all groups, except CB, had globally unidirectional metabolic \textit{off} sets in qCMR\textsubscript{glc} \textit{t}-maps, whereas regionally bidirectional differences were seen for all groups in GMN \textit{t}-maps. In addition, the hypometabolism and hypermetabolic regions identified by GMN \textit{t}-maps depict metabolic changes that are substantially smaller in magnitude (i.e., 3–6 times) than the global differences captured by the qCMR\textsubscript{glc}\textit{t}-maps (Figure S7).

### 4. Discussion

Absolute quantification of brain glucose metabolism with FDG-PET requires continuous arterial blood sampling throughout the imaging procedure [1, 39]. As arterial blood sampling in clinical settings is difficult or logistically impossible, alternative approaches are commonly used to determine relative differences among groups or conditions. The complementary approaches for quantitative PET generally involve a form of interindividual normalization, based on the ratio of dose injected and body weight as a proportional index of arterial input [40] or on the average uptake in whole brain, gray matter, or a preselected reference region inside [10] or outside [33] the brain. Moreover, there are considerations of arterialized venous sampling [41, 42] and image-derived input functions [43, 44]. The validity of any normalization approach relies on specific assumptions that usually are not readily testable, such as the linearity of the relationship between body weight and distribution volume, the expected range of metabolic changes (i.e., regional versus global), or the validity of a chosen reference region for the population being examined.

Here, we used a new validated method for deriving quantitative baseline metabolic activity from FDG-PET without individual normalization [37], but where the quantified measure of CMR\textsubscript{glc} (qCMR\textsubscript{glc}) for the HAEC condition was compared to the absolute CMR\textsubscript{glc} (aCMR\textsubscript{glc}) from Hyder et al. (aCMR\textsubscript{glc}-HYD), also for the HAEC condition [36]. The process consisted of two steps. First, an intensity transformation was computed on a per-site basis for all HAEC datasets, using the Jensen-Shannon divergence method [38], to match the distribution of voxel intensities to the aCMR\textsubscript{glc}-HYD data-base [36]. This enabled the original tissue-radioactivity values for each HAEC group to be converted to aCMR\textsubscript{glc} units on a per-site basis. This procedure also created a per-site intensity transformation that maps the original PET radioactivity counts to qCMR\textsubscript{glc}, which can be used to

<table>
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convert radioactivity values for other conditions (i.e., conditions without lesions) scanned at that site using the same scanning parameters into aCMR/gl units. Finally, we validated this procedure by comparing qCMR/gl to aCMR/gl, on a voxel-by-voxel basis using Pearson correlation and Euclidean distance for all gray matter regions between the two datasets.

Our goal was to compare glucose metabolism measured by PET from a large number of conditions, including specific levels of sedation depth induced by anesthesia, several levels of disorder of consciousness, awake/healthy with eyes open, and congenital blindness. Each cohort included a control group of healthy, awake individuals resting with eyes closed, which were all comparable across sites. The validated qCMR/gl group data led to new insights into the effects of GMN on the detection and interpretation of global versus regional metabolic estimates.

The qCMR/gl maps for all states (except the congenitally blind) revealed significant global differences relative to the eyes closed control group, which ranged in magnitude from ~10% increase for the awake, eyes open group to ~60% decrease in the unresponsive wakefulness syndrome. These global changes of qCMR/gl are in good agreement with previous findings of changes with eyes open versus eyes closed states [45, 46], congenitally blind versus healthy sighted subjects [47, 48], effects of halogenated anesthetics [49–52], and findings in disorders of consciousness [35, 53]. Specifically, various anesthetics and disorders of consciousness have largely reported globally depressed metabolism compared to the healthy condition (see references within [19, 33]).
After GMN, these large global changes were absent from the GMN t-maps due to regression to the mean value. Consequently, the GMN t-maps showed patterns of regional increase and decrease in metabolism among different states, suggesting that significant global information is not captured with the GMN procedure. Although increases/decreases were observed in congenitally blind with/without GMN, both the hypometabolic and hypermetabolic regions showed heterogeneous activities upon GMN. These results suggest that global normalization puts an overemphasis on regional differences.

4.1. GMN Eliminates Global Metabolic Changes across States.

In all conditions other than congenitally blind, we found globally unidirectional changes of qCMRglc estimates compared to the control group, with metabolic differences among states distributed within a large range (i.e., 0.14 to 0.34 μmol/g/min). In sharp contrast, GMN yielded regional increases and decreases compared to the eyes closed control group, with relative metabolic rate differences among states distributed within a narrow range (i.e., ±0.05 μmol/g/min). These results suggest that the global component of FDG-PET images contains state-dependent metabolic information that is lost upon GMN. Moreover, the present work shows that the hypometabolism and hypermetabolic regions revealed by GMN depict metabolic changes that are substantially smaller in magnitude than the inherent global metabolic differences. Although the regional pattern of deviations from the global mean of normalized FDG conveys important information about metabolic networks, exclusion
of the global mean can yield different interpretations such as the regionally increased metabolic activity to disease states, a concern previously raised in the context of neurodegenerative diseases [12, 54].

However, when absolute differences are of small magnitude and regionalized, as in the present comparison of congenitally blind to the sighted control group, images with and without GMN showed very similar patterns of hypometabolism and hypermetabolic areas. In this particular case, the GMN procedure exposed the differences only after removal of interindividual global variations, without any penalty for misrepresentation of the magnitude of the differences. Overall, these comparisons, especially with that of the congenitally blind group versus the other groups, strongly suggest that there are new insights to be gained by inclusion of both absolute and GMN analysis for PET-FDG data of neuropsychiatric and neurodegenerative diseases.

4.2. Study Limitations and Future Directions. The main limitation of the current study is the acquisition of PET-FDG images from multiple sites that were calibrated to produce qCMRglc comparisons across the different groups, thereby limiting the statistical significance of state-dependent variations. The high similarity between qCMRglc in the resting awake eyes closed (control) state across five different sites, which were nearly identical to aCMRglc region-to-region variations, suggests that qCMRglc maps from the different sites indeed were comparable. While the qCMRglc measure proved stable on a per-group basis, this report did not investigate its validity on a per-subject basis, specifically for conditions with
Table 4: Thesholding t-maps in Figures 3–6 revealed unidirectional and bidirectional changes, which is illustrated in terms of the number of positive (P) and negative (N) clusters, where they, respectively, correspond to areas of higher and lower intensities compared to control. See Table 1 for abbreviations of conditions. The positive clusters in the thresholded GMN (P_{GMN}) versus qCMR_{glc} (P_{qCMR}) t-maps were 8 times greater, whereas negative clusters in the thresholded GMN (N_{GMN}) versus qCMR_{glc} (N_{qCMR}) t-maps were 2 times greater. Similarity between thresholded GMN and qCMR_{glc} t-maps was assessed by several metrics: (i) the total number of clusters given by the sum of P and N clusters, for qCMR_{glc} (T_{qCMR} = P_{qCMR} + N_{qCMR}) and GMN (T_{GMN} = P_{GMN} + N_{GMN}) thresholded t-maps; (ii) the difference between the P clusters (D_P) for GMN and qCMR_{glc} thresholded t-maps (D_P = P_{GMN} − P_{qCMR}); (iii) the difference between the N clusters (D_N) for GMN and qCMR_{glc} thresholded t-maps (D_N = N_{GMN} − N_{qCMR}). Analysis shows that T_{GMN} was about 4 times greater than T_{qCMR}, whereas both D_P and D_N were greater than 0, signifying that GMN thresholded t-maps consistently revealed more bidirectional changes. For thresholded t-maps, see Figure S3 for EMCS, MCS, and UWS versus control (HAEC); Figure S4 for Sev0.25, Sev0.5, and Des1 versus control (HAEC); Figure S5 for HAEO versus control (HAEC); and Figure S6 for CB versus control (HAEC).

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<th>N_{qCMR}</th>
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<th>N_{GMN}</th>
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<th>T_{GMN}</th>
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Mean ± standard deviation: 0.3 ± 0.5, 1.0 ± 0.5, 2.3 ± 1.5, 1.9 ± 1.1, 1.3 ± 0.7, 4.1 ± 1.1, 2.0 ± 1.4, 0.9 ± 1.4
5. Conclusions

At present, analysis of PET data generally ignores the global baseline signal. However, both the baseline neuronal activity and the requisite energy demands supporting the activity of the cerebral cortex of awake humans are substantial [25, 26, 63]. Removing the global PET signal prior to comparison with the resting awake eyes closed (control) state exposed regionally bidirectional metabolic effects, along with some regional changes observed upon normalization. Improper use of global signal normalization may thus lead to the incorrect assignment of elevated metabolism to regions and, by inference, the presence of elevated neuronal activity despite an impaired state of consciousness. Conversely, the approach used here (i.e., without GMN) not only preserved the global alteration caused by sedation and consciousness disorders but also detected localized abnormalities in the context of the congenitally blind. In light of the current findings, we recommend that the baseline metabolic activity be included in the analysis of PET neuroimaging data, and only then is it possible to discern global and regional metabolic differences between healthy and diseased states.

Abbreviations

- BOLD: Blood oxygen level-dependent
- CBF: Cerebral blood flow
- CMR$_{glc}$: Cerebral metabolic rate of glucose metabolism
- CMR$_{O2}$: Cerebral metabolic rate of oxygen metabolism
- GMN: Global mean normalization
- MNI: Montreal Neurological Institute
- PET: Positron emission tomography

Disclosure

Garth J. Thompson’s current address is iHuman Institute, ShanghaiTech University, Shanghai 201210, China

Conflicts of Interest

The authors declare no conflict of interest.

Authors’ Contributions

Ron Kupers, Maurice Ptito, Steven Laureys, Valentin Riedl, Michael T. Alkire, Albert Gjedde, and Fahmeed Hyder conceived of, designed, and performed the research. Kristian N. Mortensen, Garth J. Thompson, Peter Herman, and Fahmeed Hyder analyzed the data. Kristian N. Mortensen, Garth J. Thompson, Peter Herman, Maxime J. Parent, Douglas L. Rothman, Johan Stender, Albert Gjedde, Ron Kupers, Maurice Ptito, Steven Laureys, Valentin Riedl, Michael T. Alkire, and Fahmeed Hyder wrote the paper.

Acknowledgments

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Supplementary Materials

Figure S1: voxel-to-voxel correlations of qCMRglc in gray matter of the human brain. Figure S2: voxel-to-voxel correlations of qCMRglc in white matter of the human brain. Figure S3: thresholded t-maps of metabolic variations in disorders of consciousness. Figure S4: thresholded t-maps of metabolic variations in anesthetic sedation. Figure S5: thresholded t-maps of metabolic variations with eyes open. Figure S6: thresholded t-maps of metabolic variations in congenital blindness. Figure S7: magnitude of metabolic variations with and without GMN. Table S1: description of human gray matter regions. (Supplementary Materials)

References


[36] F. Hyder, P. Herman, C. J. Bailey et al., “Uniform distributions of glucose oxidation and oxygen extraction in gray matter of...


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