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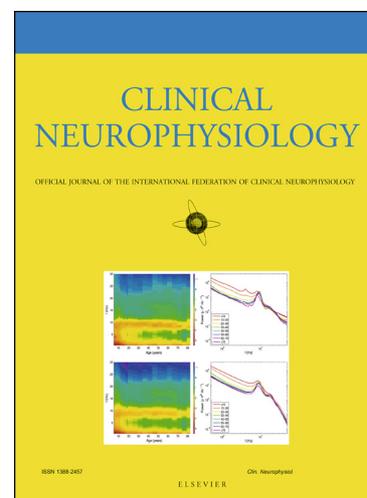
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**Defining abnormal slow EEG activity in acute ischaemic stroke:
delta/alpha ratio as an optimal QEEG index**

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ABSTRACT

Objective: Quantitative electroencephalographic (QEEG) indices sensitive to abnormal slow (relative to faster) activity power seem uniquely informative for clinical management of ischaemic stroke (IS), including around acute reperfusion therapies. However these have not been compared between IS and control samples. The primary objective was to identify the QEEG slowing index and threshold value which can most accurately discriminate between IS patients and controls.

Methods: The samples comprised 28 controls (mean age: 70.4; range: 56-84) and 18 patients (mean age: 69.3; range: 51-86). Seven indices were analysed: relative bandpower (delta, theta, alpha, beta), delta/alpha power ratio (DAR), (delta+theta)/(alpha+beta) ratio (DTABR) and Q_{SLOWING} . The accuracies of each index for classifying participants (IS or control) were analysed using receiver operating characteristic (ROC) techniques.

Results: All indices differed significantly between the samples ($p < .001$). DAR alone exhibited optimal classifier accuracy, with a threshold of 3.7 demonstrating 100% sensitivity and 100% specificity for discriminating between radiologically-confirmed, acute IS or control. DTABR and relative delta were the next most accurate classifiers.

Conclusions: DAR of 3.7 demonstrated maximal accuracy for classifying all 46 participants as acute IS or control.

Significance: DAR assessment may inform clinical management of IS and perhaps other neurocritical patients.

Keywords: Acute ischaemic stroke; quantitative electroencephalography; delta activity; alpha activity.

HIGHLIGHTS

- All QEEG indices (sensitive to power of delta, theta, alpha, and/or beta bands) differed highly significantly between acute ischaemic stroke (IS) and control samples.
- Delta/alpha power ratio (DAR) demonstrated maximal accuracy for discriminating between acute IS patients and controls.
- $DAR < 3.7$ was 100% specific for the absence, and > 3.7 was 100% sensitive for the presence, of a radiologically-confirmed IS lesion.

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INTRODUCTION

Ischaemic stroke (IS) produces abnormal, slow EEG activity - particularly in the delta frequency range (1-4 Hz) - and attenuation of normative, faster activity, particularly in the alpha frequency range (8-12 Hz; e.g., Jordan, 2004; Hirsch et al., 2013). A recent review (Finnigan and van Putten, 2013) emphasises that particular QEEG indices, which are sensitive to such cerebral pathophysiology following IS, can inform clinical decision-making including: (1) continuous monitoring to inform about the efficacy of acute reperfusion therapies, and; (2) outcome prognostication and clinical management decisions based on brief, pre-discharge EEG. As summarised in Table 1, indices sensitive to the power of delta relative to faster activity which have proven particularly informative for these clinical applications are: relative delta power (e.g., Claassen et al., 2004; Finnigan et al., 2004; 2007), the delta/alpha power ratio (DAR; e.g., Claassen et al., 2004; Finnigan et al., 2007; Leon-Carrion et al., 2009; Schleiger et al., 2014; Sheikh et al., 2013), and $(\text{delta}+\text{theta})/(\text{alpha}+\text{beta})$ power ratio (e.g., DTABR; Sheorajpanday et al., 2011 a). The current study investigates the respective capacities of these and other bandpower-derived indices to distinguish between acute IS versus normative EEG.

Several observations indicate that continuous monitoring of relative delta power or DAR can promptly inform bedside assessment of the efficacy (or otherwise) of acute reperfusion therapies, such as intravenous alteplase or intra-arterial clot retrieval, prior to potential clinical changes (e.g., Finnigan et al., 2006; Finnigan and van Putten, 2013; Sheikh et al., 2013). Importantly QEEG can thus inform about potential salvage of ischaemic neural tissue ("penumbra"), whereas imaging modalities can inform about (re-)perfusion but not the activity of this ischaemic, cerebral tissue. To date such studies have relied upon repeated-measures, statistical tests (performed retrospectively) to assess the potential significance of delta power or DAR changes over time. However such techniques are not particularly feasible in time-critical, clinical settings and for this and other reasons, identification of a QEEG threshold value for defining abnormal cerebral activity should prove informative and translatable. For example reperfusion therapy may be more readily (yet accurately) determined to be successful when a pertinent QEEG index (e.g., DAR) normalises

and remains below a critical threshold value; whereas maintenance of the QEEG index above the threshold would indicate unsuccessful therapy. More broadly, identification and usage of a QEEG abnormality threshold for cerebral ischaemia might be analogous to, for example, the diagnosis of diabetes based primarily on a fasting plasma glucose level ≥ 7.0 mmol/l. Furthermore EEG/QEEG assessment or continuous monitoring relative to such a threshold may prove pertinent not only to critically informing decisions around acute reperfusion therapies or pre-discharge prognoses (and associated decision-making) in IS, but also in other clinical applications such as detection of delayed cerebral ischaemia following subarachnoid haemorrhage (e.g., Claassen et al., 2004; Foreman and Claassen, 2012).

In general terms, it has been proposed that global DAR and/or DTABR values < 1 are relatively normative and that values higher than approximately two may be considered abnormal (Finnigan and van Putten, 2013). However these are semi-informed estimates as systematic analyses of such indices from IS patients versus controls have not been reported to date, hence normative ranges and precise abnormality thresholds for such QEEG indices remain unknown. The primary aim of the current study is to address and help resolve these knowledge gaps by performing such analyses. In addition several QEEG indices - of the power of slow relative to faster activity - have been variously analysed in IS samples (delta power, DAR, DTABR; see above) although it remains unresolved as to which is the optimal index for defining abnormal slow activity in acute IS and discriminating between the latter versus normative state; hence this was a further aim of the current study. Addressing these aims would likely help advance the utility of QEEG monitoring in acute IS treatment as well as other clinical applications. Our objectives are pursued via statistical analyses of numerous bandpower-derived QEEG indices from a sample of acute IS patients, compared to those from a sample of age-matched control participants.

METHODS

Participants and recruitment

This study was approved by the local hospital and university, human research ethics committees, and all participants (or the legally authorised, substitute decision maker for severe stroke cases, if appropriate) gave informed consent.

Healthy older adults

Participants were recruited from an older adult participant panel which was initially assembled via newspaper advertisements. All participants completed a detailed questionnaire about their own health and current medications, as well as any relevant health issues in their family. Participants with a history of anxiety, depressive disorders, head injury, stroke, epilepsy, heart attack, neurological conditions, major psychiatric disorder, were excluded from the study. Thirty older adult participants were thus recruited.

Each participant was administered the Mini Mental State Exam, Wechsler Adult Intelligence Scale (3rd edition), Geriatric Depression Scale, Boston Naming Test, Alzheimer's Disease Assessment Scale, cognitive sub-section, the Rey Auditory Verbal Learning Test, and letter (F,A,S) and category (animal) fluency tests. All participants previously had cranial magnetic resonance imaging (MRI) performed as part of a parallel study. On the basis of their outcomes from all screening and assessment items detailed above, participants were classified as controls by consensus decision between a neurologist and a clinical psychologist. Classifications were made with thorough consideration of contemporary diagnostic criteria for mild cognitive impairment (e.g., Winblad et al., 2004) and for "delirium, dementia, and amnesic and other cognitive disorders" in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (2000; DSM-IV-TR). Two participants (both male, ages 75 and 77) met criteria for mild cognitive impairment (amnesic domain; e.g., Winblad et al., 2004) hence these participants were excluded from the analyses.

As summarised in Supplementary Table S1 the normative older adult sample then included 28 healthy, cognitively unimpaired individuals (17 females) whose mean age was 70.4 years (S.D. = 8.58, Range = 56 - 84).

Stroke patients

Patients with acute focal motor neurological symptoms together with symptoms such as speech impairment, inattention or impaired cognition, consistent with ischemic cortical stroke, were initially considered for recruitment. All patients underwent acute, non-contrast computed tomography (CT) scanning. For patients 1 to 10, magnetic resonance imaging (MRI) assessments were also performed, within 6 h of symptom onset, and EEG recordings performed as soon as feasible thereafter (and always within 24 h of onset) at the bedside, as per a previously-reported protocol (Finnigan et al., 2004). Patients 11 to 18 had CT perfusion (CTP) and angiogram (CTA), and EEG recordings commenced as soon as feasible thereafter at the bedside. Ischaemic stroke and arterial territory affected by same were confirmed via acute, multi-modal MRI or CT, and thereby only patients with unilateral, ischaemic lesions in the territory of the middle cerebral artery (MCA) were included. Patients were excluded if they presented with fever, seizures, a cerebral haemorrhage on CT, a pre-existing neurological condition that would confound clinical or neuroimaging assessment, such as radiological evidence of previous stroke, EEG abnormalities consistent with encephalitis or medications that could confound EEG assessment (e.g., benzodiazepines, tricyclics or neuroleptic medications). The National Institutes of Health Stroke Scale (NIHSS) was administered by a neurologist following enrolment into the study.

Eighteen IS patients (7 males; mean age, 69.3; range, 51 to 86 years) were enrolled. Patient demographics, affected vascular territories, admission NIHSS scores, QEEG indices and descriptive statistics for same are summarised in Supplementary Table S2. (Patients 4, 6, 7 and 15 were administered intravenous alteplase following imaging and EEG.)

EEG data acquisition

An elasticated EEG cap (Quik-Cap, Neuromedical Supplies) was used containing nineteen sintered Ag/AgCl scalp electrodes positioned at the sites of the international 10-20 system (FP1, FP2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6,

O1, O2), except for patients 11 to 18 for whom individual electrodes (Nicolet) were used but with all other parameters remaining identical. Vertical and horizontal electro-oculograms (EOGs) were recorded from two bipolar channels via electrodes placed below and on the supra-orbital ridge of the left eye (VEOG) and on the outer canthus of each eye (HEOG). Electrode impedances were predominantly 5-10 kOhms or less. The online reference was immediately posterior to Cz. These data were acquired using a Neuroscan Synamps2™ amplifier or, for IS patients 11 to 18, a NicOne Brain Monitor system (Natus Medical Inc.) with a 500Hz sampling rate and were filtered online (bandpass; 0.01-100 Hz). EEG was recorded for at least fifteen minutes per participant in resting, awake state with eyes closed. Alertness or sleepiness was assessed throughout each recording, primarily via periodic behavioural assessments (saying the patient's name and asking if they were still awake, every 3 to 5 minutes). Generally, patients and control participants were awake and resting quietly with eyes closed during recording periods from which EEG data were analysed quantitatively (i.e., the first 3 to 5 minutes; see below). Two patients (3, 18) evidently were dozing by the fifth minute of recording although their QEEG data is consistent with previous evidence that in acute IS the capacities of global delta power and DAR to inform clinical assessments are robust to sleep state (Finnigan et al., 2004) and sedation (Sheikh et al, 2013), at least. That is, if sleep were to substantially increase delta power and DAR we would have expected these indices to be higher in these, relative to the other participants (see Figure 1 and Supplementary Table S2).

EEG signal processing & QEEG computations

Offline signal processing was performed with Edit 4.5 software (Compumedics-Neuroscan) using the following methods which we have previously reported (e.g., Cummins and Finnigan, 2007, 2008; Finnigan et al., 2007; Finnigan and Robertson, 2011; Schleiger et al., 2014). EOG artefacts were reduced where appropriate using the procedure of Semlitsch et al. (1986). These data were filtered (bandpass; 0.5-40 Hz, 12dB/octave), then EEG data were re-referenced to the common average reference. Each data file was "epoched" into contiguous epochs of 2048 ms (1024 data points), then epochs in which EEG amplitude exceeded $\pm 100 \mu\text{v}$ were

automatically rejected. From the first 90 epochs of artefact-free data per participant, EEG power (μV^2) was computed for each electrode using the fast Fourier Transform (FFT) with a cosine window (with tapering at beginning and end of each epoch, equating to 10% of epoch duration). Hence each QEEG index was computed from a total of 184.3 s of artefact-free, EEG data per participant. This process resulted in a power value for each 0.488 Hz iteration. From the resulting power spectra for each electrode, absolute power was summed across the delta (0.98-3.91 Hz), theta (4.39-7.32 Hz), alpha (7.81-12.21 Hz), and beta (12.70–29.79 Hz) bands (inclusive) as was done in previous studies cited above (e.g., Schleiger et al., 2014). It can be assumed that power for any one of these frequency ranges does not significantly differ from that for the respective “0.5 Hz iteration” ranges (e.g., 1-4 Hz, 4.5-7.5 Hz, etc.). Relative power for each band was computed as the ratio of summed absolute band-power to total summed power across the 0.98-29.79 Hz range. DAR and DTABR were computed as the ratios of absolute power for the respective frequency bands of interest. Q_{SLOWING} was computed as the ratio of summed power across 1.95-7.81 Hz versus summed power across 1.95-24.90 Hz (inclusive; Lodder and van Putten, 2013). These indices all were initially computed separately for each electrode, then were averaged over all nineteen scalp electrodes to create “global” QEEG indices as per previous studies (e.g., Finnigan et al., 2007; Schleiger et al., 2014; Sheikh et al, 2014).

QEEG statistical analyses

Statistical analyses were performed using SPSS Statistics (v22; IBM) and Microsoft Excel software. The following analyses were performed on all seven QEEG indices, albeit the primary foci were the four indices of abnormal slow relative to faster activity (relative delta power, DAR, DTABR, and Q_{SLOWING}). Initially, for each of these indices, descriptive statistics (means and standard deviations) for the healthy older adult sample were computed. Various normality tests were conducted, employing Q-Q and P-P probability plots, both normal and detrended normal, on “raw” as well as log-transformed data. The outcomes of these tests generally indicated that the data sufficiently satisfied assumptions of normality and moreover, that log transformation generally did not substantially alter these scenarios. Each of the seven QEEG

indices were then compared statistically between the samples via independent groups t-tests, with a Bonferroni correction for multiple comparison also employed (thus rendering the critical “alpha” level to be 0.007 or less; i.e., 0.05 divided by 7). On the basis of past literature (summarised in Finnigan and van Putten, 2013) we hypothesised that indices directly involving and proportional to delta power (relative delta, DAR, DTABR) would be significantly greater in the acute stroke sample, whereas relative alpha power would be significantly greater in the control sample. We did not consider existing literature to be of sufficient quantity and/or equivocality to support definitive hypotheses regarding relative theta or beta power, or Q_{SLOWING} .

Thereafter a preliminary abnormality threshold for each QEEG index was identified, as the “critical z” value representing a z-score of + 1.96 relative to (1.96 standard deviations above) the normative mean, for all indices except relative power of the “faster” frequency bands, alpha and beta (in which cases z-scores of - 1.96 were computed). This is a standard statistical method for defining whether or not an individual’s score is significantly different to the mean of a given sample or population (using an alpha level of 0.05, two-tailed; e.g., Howell, 2014). Using this method an individual is significantly different to a given population if the absolute value of the z-score is greater than 1.96. For five of the QEEG indices analysed (excluding alpha and beta power), relatively high values are routinely observed in IS, indicating abnormal degrees of slow activity. In addition it remains unclear as to whether or not a z-score associated with DAR, for example, of - 1.96 might be considered abnormal *per se*. Hence only “upper-end” abnormality thresholds were of key interest in the current investigation (with the exception of alpha and beta power, for which “lower-end” criteria were considered, secondarily). This is not only a routine statistical approach (e.g., Howell, 2014) but also it is analogous to that of a past study which computed z-scores from QEEG band-power measures acquired from IS patients (and correlated these with functional outcome measures; Cuspineda et al., 2003).

The respective capacities of the preliminary abnormality thresholds to accurately classify participants as ischaemic stroke or control were then analysed using

receiver operating characteristic (ROC) techniques. Classifier specificity and sensitivity values were first calculated for each preliminary threshold. For cases wherein an alternative threshold value for any given QEEG index was associated with better classifier performance on the basis of ROC results (a more optimal combination of specificity and sensitivity values) relative to the preliminary threshold, the latter was revised as appropriate.

RESULTS

Comparisons between control and acute IS samples

Descriptive statistics for age and QEEG indices of the control and IS samples are summarised in Table 2. Age did not significantly differ between the samples. QEEG indices for each individual participant are plotted in Figures 1-4 and are listed for the control and IS samples in Supplementary Tables S1 and S2 respectively. As expected all QEEG indices were higher in the stroke sample, with the exception of relative alpha and relative beta power which were higher in the control sample. Mean relative delta power was twice as high in the IS sample as in the controls whereas mean relative alpha was more than twice as high in controls as in IS and relatedly, DAR was much higher in IS. Although relative theta did not differ so markedly (being slightly higher in IS), mean relative beta power was more than twice as high in controls compared to IS and relatedly, DTABR was much higher in IS. Independent groups t-tests demonstrated that all seven QEEG indices differed highly significantly between the samples: all between-sample differences were of sufficient magnitude to maintain statistical significance even after a Bonferroni correction for multiple comparisons (see Table 2).

Receiver operating characteristic analyses

Preliminary thresholds computed for each QEEG index, corresponding to the values at which $z = +1.96$ or in the case of relative power for the “faster” bands (alpha and beta), $z = -1.96$, are summarised in Table 2. The outcomes of initial ROC analyses of classifier performance of these thresholds are summarised in Supplementary Table S3. In brief, DAR demonstrated optimal classifier performance as indicated by an area under the ROC curve (AUC) value of 1 (the maximum possible AUC value).

This result relates to the fact that DAR was the only index for which there was separation (i.e., no overlap) in values between the two samples (see Figure 2, compared to Figures 3 and 4). The next most accurate classifier indices according to their respective AUC values were DTABR (0.996) and relative delta power (0.994), while the poorest classifier clearly was relative theta (0.812). None of the preliminary thresholds demonstrated maximal classifier accuracy, in terms of both sensitivity and specificity measures. Although DAR had maximal performance (AUC of 1) the preliminary DAR threshold (3.32) was lower than the DAR values (3.43 and 3.56) of two control participants (C17, C26) and these “false positives” are reflected in the specificity of this threshold being less than 100% (Supplementary Table S3). Assuming these control participants are without occult cerebral infarction or other neurological damage, these results suggest that a higher DAR threshold would be appropriate. Likewise for all indices except DTABR, revised threshold values were found to result in improved sensitivity and/or specificity, compared to the preliminary thresholds (see Table 3). A DAR threshold of 3.7 demonstrated 100% specificity and 100% sensitivity (i.e., maximal accuracy) for classifying all 46 participants as (radiologically-confirmed) acute IS or control. As illustrated in Figure 2, this DAR threshold is midway between the highest control (3.56) and the lowest IS patient value (3.85). Of the six other indices the next most accurate performance was provided by the original DTABR threshold of 1.76 (100% sensitivity, 96.4% specificity) and relative theta still demonstrated the lowest accuracy as a classifier (see Table 3).

DISCUSSION

These are the first reported analyses of QEEG indices compared between acute ischaemic stroke (IS) and age-matched control samples and of DAR and Q_{SLOWING} in control participants, to our knowledge. All seven QEEG indices analysed - relative bandpower, and ratio measures of relative intensity of abnormal slow-wave activity - differed significantly between the samples. IS sample EEGs contained greater intensity of pathophysiological, slow activity (particularly delta, and also theta) relative to faster activity (particularly alpha, and also beta), whereas the converse was true for controls. In addition we statistically analysed the capacities of these

respective indices to classify EEG as acute IS or normative state. DAR was found to be the most accurate index for discriminating between radiologically-confirmed, acute IS and age-matched controls and we identified 3.7 as the optimal DAR threshold value for this purpose (see Figure 2).

Sheorajpanday et al. (2011b) proposed that DTABR < 1 was 100% specific for the absence, and > 3.5 was 100% sensitive for the presence, of a recent, radiologically-confirmed IS lesion (DAR was not analysed). Those findings do not resolve how to interpret DTABR values between 1 and 3.5 and this is salient, for in the current data 6 IS cases (33%) and 9 controls (32%) were within this range. The current outcomes update this scenario by indicating that DAR is a more accurate classifier index; DAR < 3.7 is 100% specific for the absence, and > 3.7 is 100% sensitive for the presence, of a recent, radiologically-confirmed IS lesion. The sample of middle cerebral artery IS patients included several cases with relatively small ischaemic lesions on imaging and mild symptoms (cases 1, 2, 6; Table 2) as well as a subcortical lesion (see below) suggesting this threshold may apply to all such cases. However analyses of data from larger samples may identify a revised threshold and/or thresholds more specific to stroke locations (e.g., cortical versus subcortical; anterior versus posterior circulation).

The efficacy of DAR compared to other QEEG indices

These outcomes converge with and build upon other evidence supporting the value of DAR, over other QEEG indices, for assessing ischaemic cerebral pathophysiology (see Table 1). DAR previously was found to be the most effective of 12 QEEG indices in relation to detection of delayed cerebral ischaemia in subarachnoid haemorrhage (Claassen et al., 2004). Indices analysed included absolute and relative bandpower, power ratios and also alpha and delta coherence. The only studies which have compared the prognostic capacities of DAR and DTABR within samples have found DAR to be superior (Finnigan et al., 2007; Leon-Carrion et al., 2009; Table 3). DTABR, relative power indices and, in part, Q_{SLOWING} (see below) are sensitive to power of all four traditional frequency bands but DAR is computed from absolute power of delta and alpha activity only. Theta and beta activity appear

relatively less reliable in IS assessments (e.g., Finnigan and van Putten, 2013; Sainio et al., 1983). For example beta is more susceptible to contamination by electromyogram (EMG) artefacts (e.g., Finnigan et al., 2007) and theta power is an unreliable index of IS pathophysiology in part because theta band measures can be confounded by slowed alpha activity (Nuwer et al., 1987). Consistent with this, in the current analyses relative theta power had the lowest accuracy as a classifier index. These factors evidently explain why several studies' results converge to indicate that DTABR is less accurate than DAR, in relation to informing IS assessments and prognoses. The optimality of DAR is exemplified by control participant C02 whom had abnormal values on all indices except DAR (e.g., higher DTABR and Q_{SLOWING} than IS Patient 2; Supplementary Table S1, Figure 1) thus only DAR (with threshold of 3.7) would correctly classify C02 as non-IS. Evidently these outcomes relate to C02 having the lowest relative beta power of the controls, whereas DAR is the only index not sensitive to beta, or theta activity. Consequently DTABR had lower classifier accuracy and specificity than DAR, albeit DTABR was overall the second most accurate index as a classifier.

In contrast to DTABR, relative power measures for delta and alpha are only indirectly sensitive to theta and beta power. In IS studies wherein EEG was recorded at 48 h or later post-stroke, relative alpha power has demonstrated highly significant correlations with functional outcome measures (Finnigan et al., 2007; Schleiger et al., 2014). However relative alpha appears less informative in relation to acute (< 24 h) IS assessment and monitoring. In terms of relative delta there was minor overlap between the samples, and the IS mean was double that of the control sample. Delta power measures have demonstrated some degree of value in IS monitoring and prognostication (Finnigan et al., 2004, 2006, 2007, 2008; Schleiger et al., 2014; see Table 1) and according to Foreman and Claassen (2012) "the relative delta (power) percentage appears to provide the most robust correlation with CBF and metabolism during focal ischemia" (compared to relative power of the other three classical frequency bands rather than to ratios such as DAR, evidently). Relative delta had similar classifier accuracy to DTABR but with slightly lower sensitivity. In future

applications one of these indices could in some cases be considered, as supplementary to DAR, for example if DAR were around the threshold.

Q_{SLOWING} was a less accurate classifier than DAR, DTABR and relative delta, with 39% of controls and 33% of patients were within the range of overlap of Q_{SLOWING} values between samples (Figure 3). Albeit it should be noted that Lodder and van Putten initially proposed Q_{SLOWING} not for this application, but as one of five indices to supplement visual EEG interpretations. In acute IS a “lower delta” power peak (around 1.5 Hz) appears salient and informative for acute IS monitoring (Finnigan et al. 2004) yet Q_{SLOWING} is not sensitive to this but measures the relative power of “upper delta and theta” activity (2-8 Hz). These factors, together with evidence that theta power is unreliable in this context (see above) appear to underlie the current findings.

Potential clinical applications of DAR abnormality assessment

Some current clinical systems automatically compute and instantly display QEEG indices (as well as conventional EEG), hence the proposed abnormality assessment employing a DAR threshold can readily be applied at the bedside. This procedure may prove valuable for promptly detecting cerebral ischaemia after subarachnoid haemorrhage (Claassen et al., 2004), in other acute brain injury or ICU patients (e.g., Foreman and Claassen, 2012; Gaspard et al., 2013; Claassen et al., 2014) or during carotid endarterectomy. Pending the outcomes of future studies, it may prove useful in other clinical contexts or neurological patient groups, such as distinguishing IS versus stroke mimic or medically unexplained symptoms.

Another potential clinical application is continuous monitoring to inform decisions regarding reperfusion therapies in acute IS. Identification of a DAR abnormality criterion extends previous proposals on this topic (Finnigan and van Putten, 2013). Sheikh et al (2013) report longitudinal DAR measures from two patients receiving reperfusion therapy. In one case (admission NIHSS score 15) DAR was above 12 prior to intravenous alteplase administration and remained highly abnormal thereafter, accurately indicating lack of successful therapy (discharge NIHSS score

11; moderate-severe disability at 3 months). In the other case DAR remained abnormal (>7.5) and symptoms severe (NIHSS 19) following unsuccessful, intravenous alteplase, but soon after ensuing intra-arterial clot retrieval DAR had dropped below 3.7, accurately indicating successful reperfusion (mild symptoms at discharge; NIHSS 2). These data indicate that DAR falling below our proposed criterion may prognosticate treatment efficacy; whereas lack of prompt DAR normalisation following intravenous alteplase (indicating unsuccessful treatment) may expedite decisions regarding intra-arterial reperfusion strategies within the critical, brief window of opportunity for same. Further data are required to systematically evaluate these proposals and identify the precise nature of DAR decrease that would reliably indicate efficacy (e.g., 4 to 3.5, versus 12 to 4, etc.). We do not suggest that QEEG could replace neuroimaging techniques in clinical management of IS, however while imaging can indicate reperfusion it does not directly inform about potential response of ischaemic, neural tissue to same. Whereas EEG directly measures neural (dys)function and the latter, and DAR may constitute a reliable, bedside indicator of success of reperfusion therapy.

Additional considerations

Several caveats to the current study should be noted. Fifteen (83%) of the IS sample had EEG performed within 8 h of stroke symptom onset and three, between 8 and 24 h. Whereas in our past studies of EEG acquired around 48 h post-onset or thereafter (Finnigan et al., 2007; Schleiger et al., 2014) DAR values below 3.7 were not uncommon, indicating that this proposed threshold is not directly applicable by this time period (albeit this is well beyond the therapeutic window for reperfusion). Future studies may further investigate a lower DAR abnormality criterion pertinent to the (pre-discharge) days following stroke which, together with other assessments, may help inform clinical prognoses and decisions. All patients studied suffered radiologically-confirmed, MCA stroke with (partly) cortical lesions in all but one case: in patient 12 the lesion was striatocapsular (restricted to the basal ganglia). While this single case suggests our proposals might also apply to such cases of IS affecting only subcortical regions (e.g., basal ganglia or lacunar strokes) or non-MCA arterial territories (see also Finnigan and van Putten, 2013) further investigations are

warranted. It is also noteworthy that subtle slowing of the peak alpha frequency can occur with ageing (e.g., Finnigan and Robertson, 2011) hence these data from participants aged 51 to 86 may possibly differ to those from younger adults. Relatedly it is possible that one or more patients had DAR above 3.7 prior to IS due to alpha slowing or cognitive impairment linked to cerebrovascular issues, for example. Other QEEG indices may also prove informative. Inter-hemispheric voltage (a)symmetry has been quantified (across 1-25 Hz) via the pairwise-derived brain symmetry index (pdBSI). To date indices relating to delta power, particularly DAR, generally have demonstrated greater value in relation to IS assessments (e.g., Claassen et al., 2004; Finnigan and van Putten, 2013; Foreman and Claassen 2012; Leon-Carrion et al., 2009; Schleiger et al., 2014; Table 1) although subacute pdBSI seems informative for outcome prognostication (e.g., Sheorajpanday et al., 2011). The only study which has directly compared subacute DAR and pdBSI reported that only DAR had highly significant correlations with functional outcomes (Schleiger et al., 2014), although future studies may investigate the potential value of pdBSI in acute IS.

Assessment of EEG traces remains important, e.g. for verification of artefacts. Lodder and van Putten (2013) report several bandpower-derived QEEG indices which can support and improve inter-rater reliability of visual EEG interpretation. As discussed in detail elsewhere (e.g., Finnigan and van Putten, 2013; Foreman and Claassen, 2012) EEG/QEEG may be susceptible to factors including artefacts, medications, metabolic conditions and sleep state, although evidence indicates that in acute IS the monitoring and prognostic value of global delta power and DAR are robust to sleep state (Finnigan et al., 2004) and sedation (Sheikh et al, 2013), at least. Nevertheless such factors must be considered, particularly given that some artefacts (e.g., those caused by eye blinks) can potentially affect delta power measures, and this further emphasises the value of assessing raw EEG traces as well as QEEG. It has been proposed that computer-assisted EEG/QEEG monitoring can facilitate recognition of common EEG abnormalities by non-expert clinical staff (Cloostermans et al., 2011). Using such technology in future, non-experts (e.g., allied health professionals) may generally prefer to first assess QEEG information (and

perhaps then consult EEG traces, or experts) whereas the converse may generally apply for experts (e.g., neurologists).

In summary DAR with a threshold value of 3.7 demonstrated perfect accuracy for distinguishing between acute IS pathophysiology and normative state, and classifying all 46 participants accordingly. Further investigations are warranted in IS and other neurocritical patient groups.

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Conflict of Interest

None.

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REFERENCES

- Claassen J, Hirsch LJ, Kreiter KT, Du EY, Connolly ES, Emerson RG, et al. Quantitative continuous EEG for detecting delayed cerebral ischemia in patients with poor-grade subarachnoid hemorrhage. *Clin Neurophysiol* 2004;115:2699-2710.
- Claassen J, Vespa P, Participants in the International Multi-disciplinary Consensus Conference on Multimodality Monitoring. Electrophysiologic monitoring in acute brain injury. *Neurocrit Care*. 2014;21(S2):129-47.
- Cloostermans MC, de Vos CC, van Putten MJ. A novel approach for computer assisted EEG monitoring in the adult ICU. *Clin Neurophysiol* 2011;122:2100-2109.
- Cummins TAD, Finnigan S. Theta power is reduced in healthy cognitive ageing. *Int J Psychophysiol*. 2007;66:10-17.
- Cummins TAD, Broughton M, Finnigan S. Theta oscillations are affected by mild cognitive impairment (amnestic domain) and cognitive load. *Int J Psychophysiol*. 2008;70:75-81.
- Cuspineda E, Machado C, Aubert E, Galan L, Llopis F, Avila Y. Predicting outcome in acute stroke: A comparison between QEEG and Canadian Neurological Scale. *Clin Electroencephalogr* 2003;34:1-4.
- de Vos CC, van Maarseveen SM, Brouwers PJ, van Putten MJ. Continuous EEG monitoring during thrombolysis in acute hemispheric stroke patients using the brain symmetry index. *J Clin Neurophysiol*. 2008;25:77-82.
- Finnigan SP, Rose SE, Walsh M, Griffin M, Janke AL, McMahon KL, et al. Correlation of quantitative EEG in acute stroke with 30 day NIHSS score: Comparison with diffusion and perfusion MRI. *Stroke* 2004;35:899-903.

Finnigan SP, Rose SE, Chalk JB. Rapid EEG changes indicate reperfusion after tissue plasminogen activator injection in acute ischaemic stroke. *Clin Neurophysiol.* 2006;117:2338-2339.

Finnigan SP, Walsh M, Rose SE, Chalk JB. Quantitative EEG indices of sub-acute ischaemic stroke correlate with clinical outcomes. *Clin Neurophysiol.* 2007;118:2525-2532.

Finnigan SP, Rose SE, Chalk JB. Contralateral hemisphere delta EEG in acute stroke precedes worsening of symptoms and death. *Clin Neurophysiol.* 2008;119:1690-1694.

Finnigan S, Robertson IH. Resting EEG theta power correlates with cognitive performance in healthy older adults. *Psychophysiology.* 2011;48:1083-7.

Finnigan S, van Putten MJAM. EEG in ischaemic stroke: Quantitative EEG can uniquely inform (sub-)acute prognoses and clinical management. *Clin Neurophysiol.* 2013;124:10-9.

Foreman B, Claassen J. Quantitative EEG for the detection of brain ischemia. *Critical Care* 2012;16:216-25.

Gaspard N, Manganas L, Rampal N, Petroff OAC, Hirsch LJ. Similarity of lateralized rhythmic delta activity to periodic lateralized epileptiform discharges in critically ill patients. *JAMA Neurol.* 2013;70:1288-1295.

Hirsch LJ, LaRoche SM, Gaspard N, Gerard E, Svoronos A, Herman ST, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. *J Clin Neurophysiol* 2013;30:1-27.

Howell DC. *Fundamental statistics for the behavioral sciences.* 8th ed. Belmont, Calif.: Wadsworth, Cengage Learning; 2014.

Jordan KG. Emergency EEG and continuous EEG monitoring in acute ischemic stroke. *J Clin Neurophysiol*. 2004;21:341-352.

Leon-Carrion J, Martin-Rodriguez JF, Damas-Lopez J, Barroso y Martin JM, Dominguez-Morales MR. Delta-alpha ratio correlates with level of recovery after neurorehabilitation in patients with acquired brain injury. *Clin Neurophysiol* 2009;120:1039-1045.

Lodder SS, van Putten MJAM. Quantification of the adult EEG background pattern. *Clin Neurophysiol* 2013;124:228-37.

Nuwer MR. EEG in the emergency department: Speeding the patients toward the right treatment plans. *Clin Neurophysiol* 2012;123:855.

Nuwer MR, Jordan SE, Ahn SS. Evaluation of stroke using EEG frequency analysis and topographic mapping. *Neurology* 1987;37:1153-1159.

Sainio K, Stenberg D, Keskimäki I, Muuronen A, Kaste M. Visual and spectral EEG analysis in the evaluation of the outcome in patients with ischemic brain infarction. *Electroencephalogr Clin Neurophysiol* 1983;56:117-124.

Schleiger E, Sheikh N, Rowland T, Wong A, Read S, Finnigan S. Frontal EEG delta/alpha ratio and screening for post-stroke cognitive deficits: the power of four electrodes. *Int J Psychophysiol*. 2014;94:19-24.

Sheikh N, Wong A, Read S, Coulthard A, Finnigan S. QEEG may uniquely inform and expedite decisions regarding intra-arterial clot retrieval in acute stroke. *Clin Neurophysiol* 2013;124:1913-4.

Sheorajpanday RV, Nagels G, Weeren AJ, van Putten MJ, De Deyn PP. Quantitative EEG in ischemic stroke: Correlation with functional status after 6 months. *Clin Neurophysiol* 2011 a;122:874-883.

Sheorajpanday RV, Nagels G, Weeren AJ, De Deyn PP. Quantitative EEG in ischemic stroke: Correlation with infarct volume and functional status in posterior circulation and lacunar syndromes. *Clin Neurophysiol* 2011 b;122:884-890.

Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund L-O, et al. Mild cognitive impairment – beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Int Med*. 2004;256:240–246.

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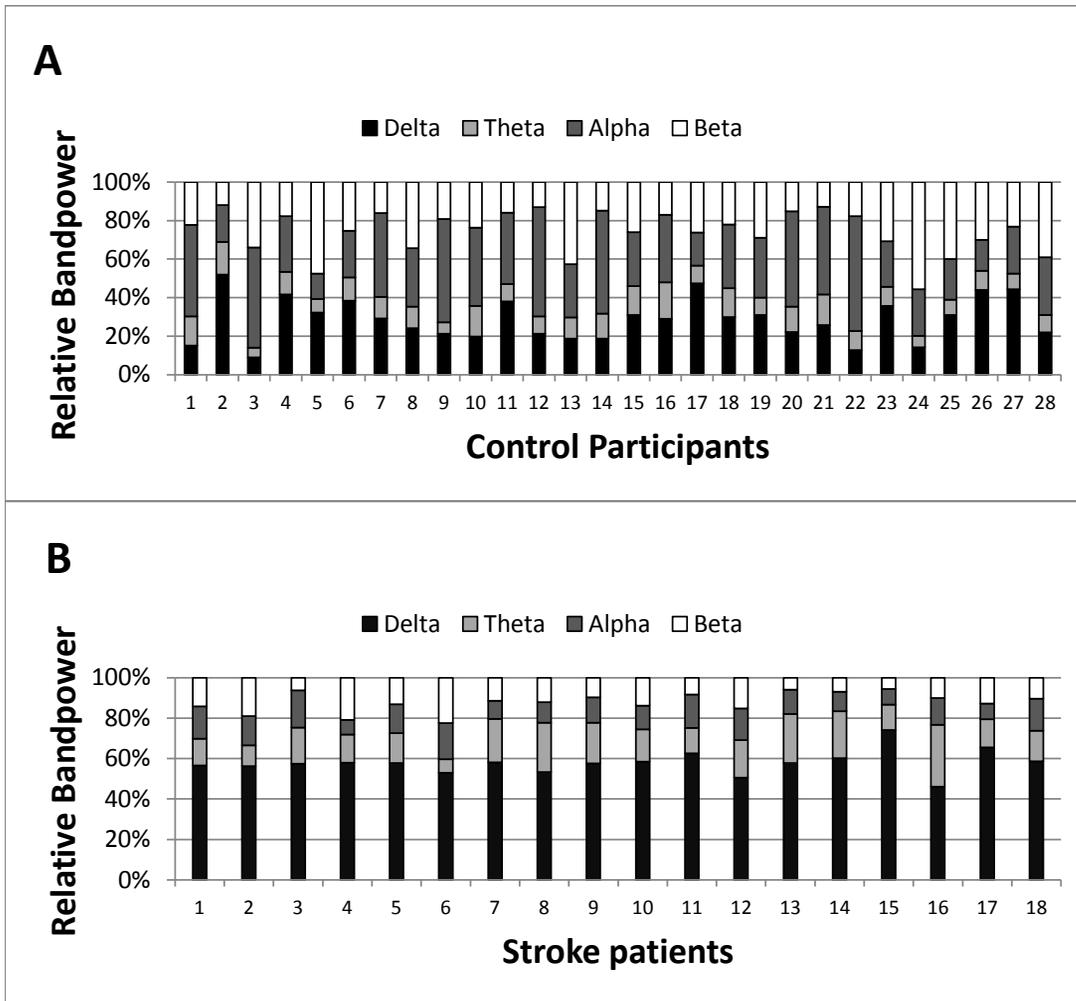
FIGURE LEGENDS

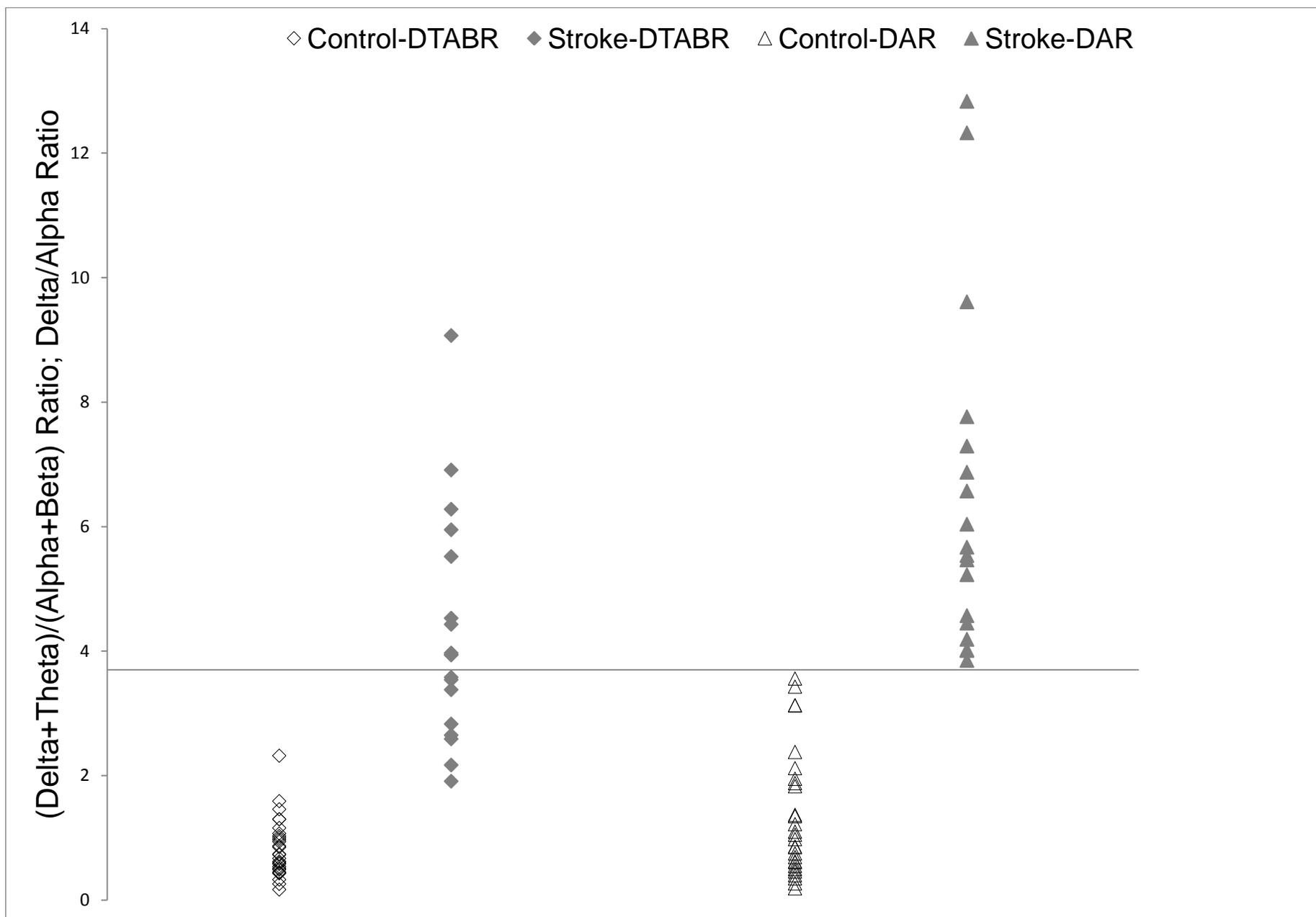
Figure 1: Bar graphs plotting relative power values for each of the four classical frequency bands in each individual analysed. A: Control participants; B: Acute ischaemic stroke cases; C: Mean values for each sample. The sample mean graphs illustrate key differences particularly for delta and alpha power. Relative delta power was significantly higher in the stroke ($M = 0.58$) than the control sample ($M = 0.29$ $t = 11.63$, $p < 0.0001$), whereas relative alpha power was significantly lower in the stroke ($M = 0.13$) than the control sample ($M = 0.34$; $t = 8.06$, $p < 0.0001$). Such outcomes also relate to the finding that DAR was significantly higher in the stroke ($M = 6.64$) than the control sample ($M = 1.34$; $t = 7.75$, $p < 0.0001$).

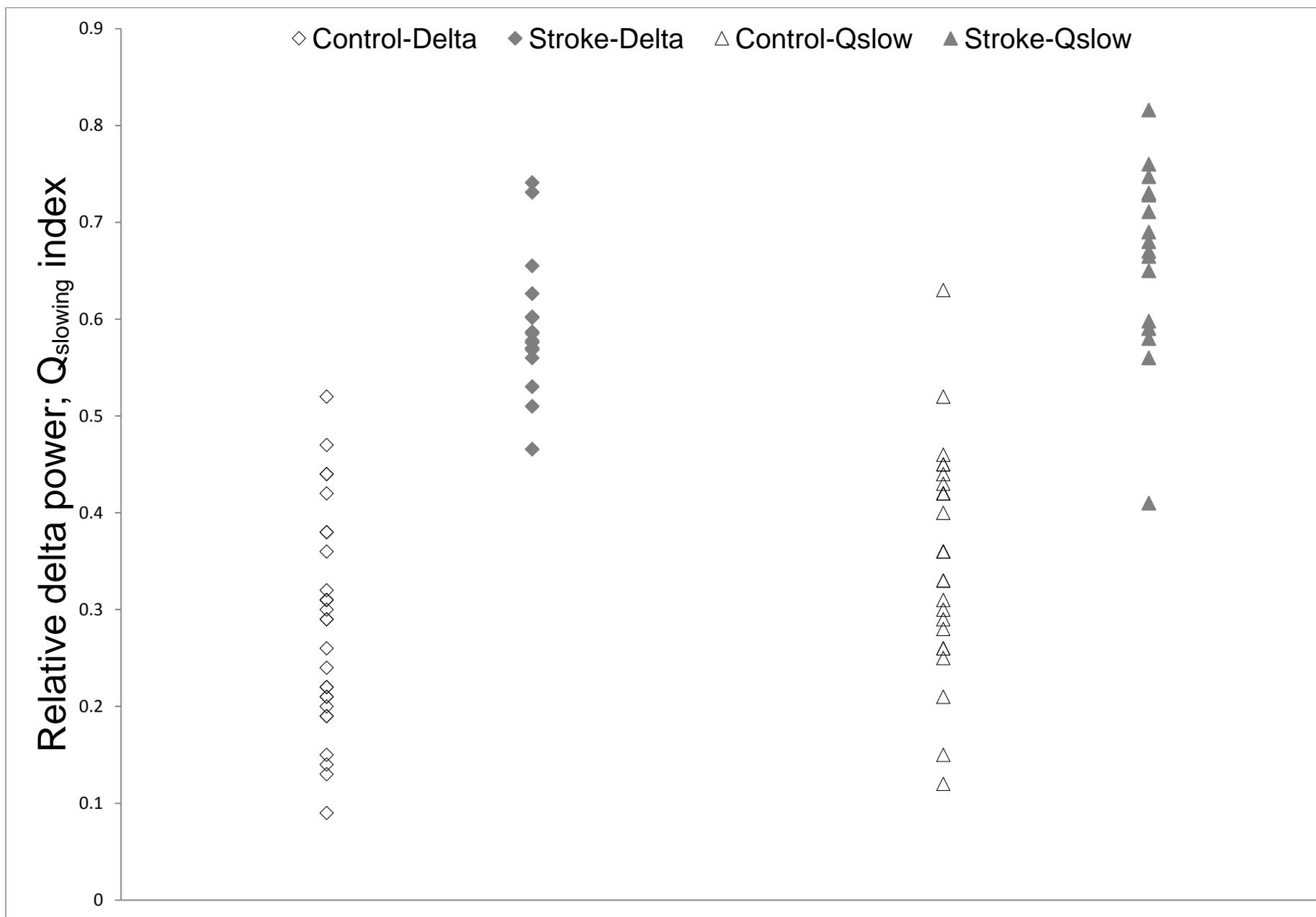
Figure 2: DTABR and DAR values plotted for each individual in the control versus stroke samples. There was substantial overlap of DTABR values between the samples but no overlap for DAR. The horizontal line represents the proposed DAR abnormality threshold value of 3.7.

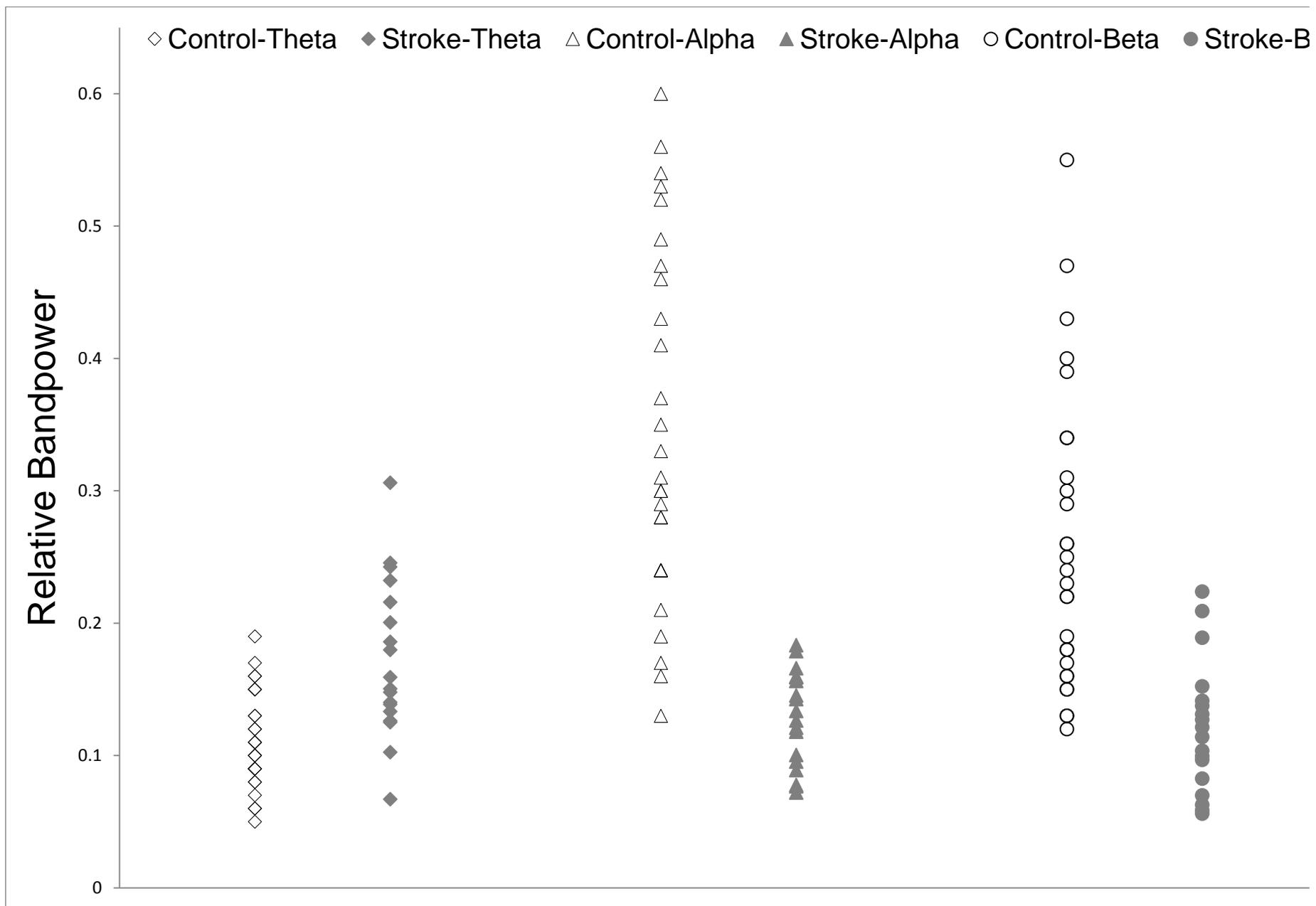
Figure 3: Relative delta power and Q_{SLOWING} values plotted for each individual in the control versus stroke samples. There was substantial overlap of Q_{SLOWING} values between the samples, and some (lesser) overlap of relative delta values.

Figure 4: Relative power values – for theta, alpha and beta bands respectively - plotted for each individual in the control versus stroke samples. There was substantial overlap between the samples for each of these relative bandpower measures.









| <u>Study</u> | <u>EEG time</u> | <u>Principal EEG/QEEG indices of prognostic value</u> | <u>Associated outcome assessment & time-point</u> |
|-----------------------------|------------------------|---|---|
| Sainio et al (1983) | < 48 h | Delta power, alpha power | Neurological examination; Discharge |
| Claassen et al (2004) | 1- 6 days [^] | DAR* | Delayed cerebral ischaemia; 14 days [^] |
| Finnigan et al (2004) | < 18 h | Delta power change over time* | NIHSS; 30 days |
| Finnigan et al (2006) | 0.5 h [#] | Delta power change over time* | Efficacy of reperfusion therapy; discharge & 90 days |
| Finnigan et al (2007) | 46-52 h | DAR*; relative alpha*; DTABR (ns) | NIHSS; 30 days |
| Finnigan et al (2008) | < 25 h | Delta power (contralateral hemisphere)* | Death; 2 - 10 days |
| Leon-Carrion et al (2009) | < 1 wk | DAR*; DTABR (ns); pdBSI (ns) | Functional Independence Measure + Functional Assessment Measure; 6 mths |
| Sheorajpanday et al (2011a) | < 72 h [†] | DTABR* pdBSI* | Modified Rankin scale; dependency, mortality; 6 mths Modified Rankin scale; disability; 6 mths |
| Sheorajpanday et al (2011b) | < 72 h [†] | DTABR* pdBSI* | Modified Rankin scale; 7 days Radiologically-confirmed stroke; < 96 h |
| Sheikh et al (2013) | 2.5 h [#] | DAR change over time* | Efficacy of reperfusion therapy; discharge & 90 days |
| Schleiger et al (2014) | 62-101 h | DAR*; relative alpha*; pdBSI (ns) | Functional Independence Measure + Functional Assessment Measure; 70-209 days |

Table 1: Summary of key details and results from past studies reporting analyses of respective QEEG indices in stroke patient samples.

* Statistically significant; (ns): non-significant

[^]Post-subarachnoid haemorrhage

[†] 96 of 110 of patients had EEG in < 72 h; the remainder in < 7 days

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| | Age | Delta | Theta | Alpha | Beta | DAR | DTABR | Q _{SLOWING} |
|-----------------------|------|----------|---------|----------|----------|----------|----------|----------------------|
| <u>Control</u> | | | | | | | | |
| Mean | 70.4 | 0.29 | 0.11 | 0.34 | 0.26 | 1.34 | 0.84 | 0.36 |
| SD | 8.60 | 0.11 | 0.04 | 0.13 | 0.11 | 1.01 | 0.47 | 0.11 |
| z _{critical} | | 0.50 | 0.19 | 0.09 | 0.04 | 3.31 | 1.75 | 0.57 |
| <u>Stroke</u> | | | | | | | | |
| Mean | 69.3 | 0.58 | 0.17 | 0.13 | 0.12 | 6.64 | 4.25 | 0.66 |
| SD | 9.9 | 0.06 | 0.06 | 0.04 | 0.05 | 2.78 | 1.77 | 0.09 |
| <i>t</i> | 0.37 | 11.63 | 3.92 | -8.06 | -5.66 | 7.75 | 8.01 | 9.98 |
| <i>p</i> | 0.71 | < 0.0001 | < 0.001 | < 0.0001 | < 0.0001 | < 0.0001 | < 0.0001 | < 0.0001 |

Table 2: Descriptive statistics of the control and stroke samples, and the outcomes of comparisons between these.

QEEG relative band-power, and power ratio, indices, and statistical (*t* and probability [*p*]) values are shown.

DAR: Delta/Alpha Power Ratio; DTABR: (Delta+Theta)/(Alpha+Beta) Power Ratio; SD: Standard Deviation

| <u>Index</u> | <u>Threshold</u> | <u>AUC</u> | <u>Sensitivity</u> | <u>Specificity</u> |
|-----------------|------------------|------------|--------------------|--------------------|
| Delta | 0.49 | 0.994 | 0.944 | 0.964 |
| Theta | 0.12 | 0.812 | 0.889 | 0.679 |
| Alpha | 0.17 | 0.972 | 0.889 | 0.929 |
| Beta | 0.16 | 0.901 | 0.833 | 0.821 |
| DAR | 3.70 | 1.000 | 1.000 | 1.000 |
| DTABR | 1.76 | 0.996 | 1.000 | 0.964 |
| Qslowing | 0.54 | 0.968 | 0.944 | 0.964 |

Table 3: Outcomes of ROC analyses for respective QEEG indices and their optimised thresholds.

DAR: Delta/Alpha Power Ratio; DTABR: (Delta+Theta)/(Alpha+Beta) Power Ratio; AUC: Area Under Curve.