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Invited review

EEG in ischaemic stroke: Quantitative EEG can uniquely inform (sub-)acute prognoses and clinical management

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HIGHLIGHTS

- Quantitative electroencephalographic (QEEG) abnormality indices sensitive to power of slow relative to faster activity, or to interhemispheric asymmetry, can uniquely inform clinical prognoses and management during (sub-)acute ischaemic stroke.
- Continuous bedside monitoring of these QEEG indices during thrombolytic therapy may instantaneously inform clinicians about the efficacy of same and thereby inform decisions about "bridging" protocols involving intra-arterial interventions.
- Current clinical EEG systems compute and display various QEEG indices, facilitating non-expert EEG interpretation. Hence wider utilisation of such technology appears warranted and would address a key stroke management objective proposed by numerous stroke opinion leaders.

ABSTRACT

Investigations of (sub-)acute ischaemic stroke (IS) employing quantitative electroencephalographic (QEEG) methods, in concert with other assessments, are reviewed. Numerous outcomes from hundreds of patients collectively indicate that (sub-)acute QEEG indices from standard systems can uniquely inform clinical management, particularly prognostication of outcomes from IS. Two classes of QEEG indices have proven particularly informative. The first quantifies the power of abnormal, slow activity relative to that of faster activity and the second, interhemispheric voltage asymmetry (broadband). Both have been identified as statistically significant predictors of outcomes assessed (via routine clinical scales) in the weeks and months following IS. Furthermore both have demonstrated higher predictive value than concomitant neurological assessments and scales, and to improve upon outcome prediction afforded by neuroimaging alone. These indices also may continuously provide unique, real-time insights into the efficacy of thrombolytic therapy, prior to clinical changes. Two key applications of QEEG which should prove valuable for future clinical management of IS are: (1) continuous, acute monitoring to inform about the efficacy of thrombolysis and decisions about potential additional interventions, and; (2) brief, subacute recording to inform outcome prognostication and clinical decisions about, for example, rehabilitation strategies. Ongoing research and technological developments will continue to facilitate clinical translation of QEEG investigations reviewed herein.

Contents

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1. Introduction: EEG and QEEG methods applied to ischaemic stroke

The human brain accounts for approximately 20% of resting oxygen consumption. If regular supply of oxygen and glucose is limited, neural function is suppressed within 20–60 s, primarily resulting from suppression of synaptic functions (Symon et al., 1977; Hofmeijer and van Putten, 2012). If energy supplies are restored within a few minutes, changes are completely reversible (Krnjevic, 2008). However, prolonged ischaemia, lasting beyond a few minutes, leads to depolarisation and cell swelling resulting from influx of ions and water (Rothman et al., 1987). Together with a large rise in cytoplasmic calcium and accumulation of free radicals, this eventually results in irreversible neuronal damage (Starkov et al., 2004). Some neurons are more vulnerable than others, and a regional variation in susceptibility exists, as well: the cerebral cortex and striatum are more sensitive than the thalamus, and the thalamus in turn is more sensitive than the brainstem.

As the electroencephalogram (EEG) reflects extracellular currents mainly resulting from excitatory and inhibitory postsynaptic currents in dendrites of cortical pyramidal cells (e.g., Nunez and Srinivasan, 2006) it is very sensitive for detecting cerebral ischaemia, hence various EEG abnormalities typically manifest following ischaemic stroke (IS).

Rapid appearance of high-amplitude, slow activity in the delta frequency range (1–3 Hz, typically) is highly typical in IS. Delta activity was found to have the strongest correlation with regional cerebral blood flow (rCBF) when compared to numerous features analysed in EEG from supratentorial, unilateral cerebral infarction patients, (Tolonen and Sulg, 1981). In middle cerebral (MCA) and internal carotid artery strokes delta activity is typically most pronounced at ipsilateral, fronto–temporo–central electrodes (Luu et al., 2001; Niedermeyer, 2003; Finnigan et al., 2004, 2007, 2008; Phan et al., 2012; see Fig. 1). At intermediate levels of ischaemia prior to appearance of delta, attenuation of beta (14–30 Hz, typically) followed by slowing of alpha (8–13 Hz, typically) activity may also occur (e.g., Jordan, 2004).

The clinical utility of EEG in has been widely reported over the past seven decades. A comprehensive review of such studies proposed that "EEG adds value to early diagnosis, outcome prediction, patient selection for treatment, clinical management, and seizure detection in acute IS" (Jordan, 2004).

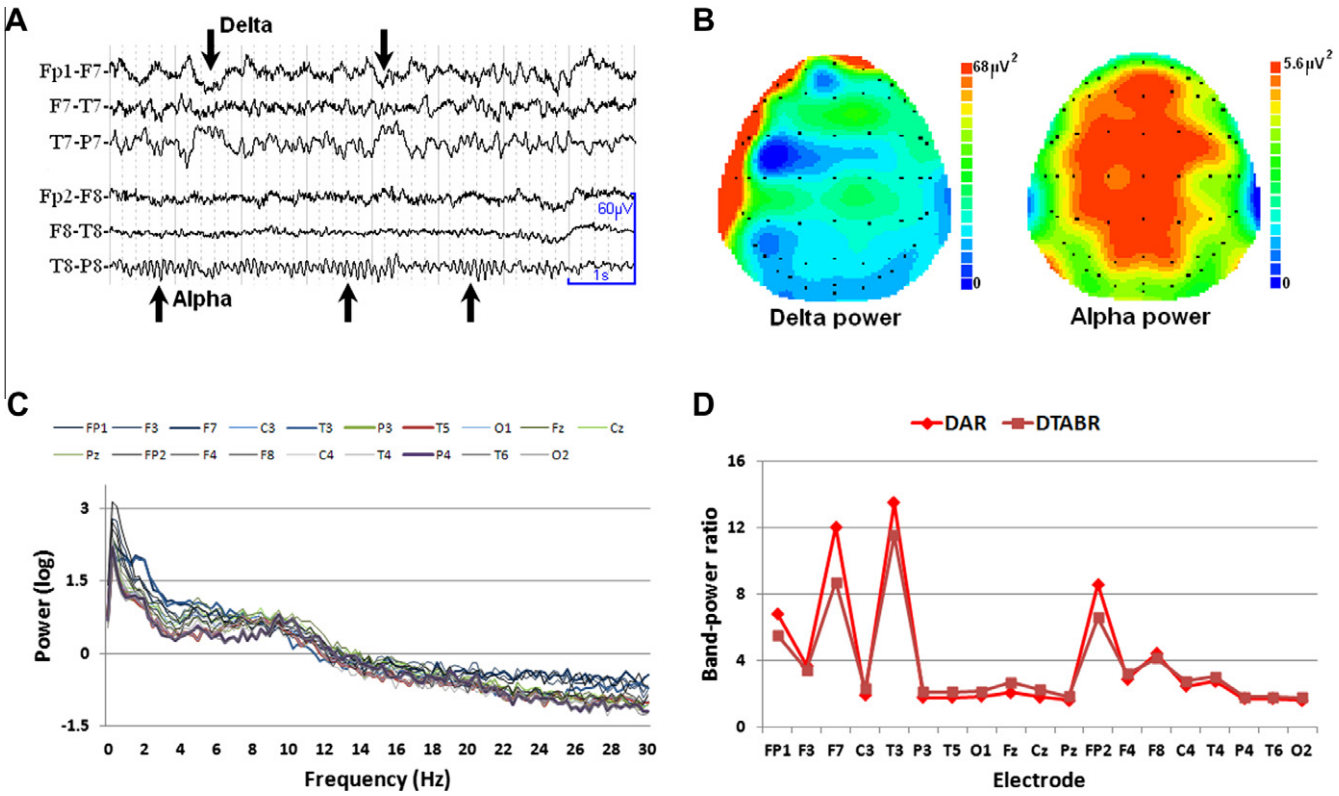

Fig. 1. EEG and QEEG data from an acute stroke patient. These data were acquired from a 57-year old woman, approximately 7 h after the onset of symptoms associated with ischaemic stroke in the left middle cerebral artery territory. The NIHSS score was 7 immediately prior to the EEG recording. (A) Raw EEG trace showing delta activity most particularly at ipsilateral channels incorporating frontal and temporal electrodes. (B) Maps illustrating the topography or distribution of mean delta (left) and alpha (right) power across the scalp (viewed from above). Note the differential power scales for delta versus alpha. (C) Power spectra plotting power (log-transformed) values across the 0–30 Hz range for each electrode of the international 10–20 system. Note the delta activity 'peak' at approximately 1.5–2 Hz, particularly at electrodes F7 and T3. Also note alpha power values at some electrodes, e.g. electrode P4, between approximately 9–11 Hz. (D) Delta/alpha ratio (DAR) and (delta + theta)/(alpha + beta) power ratio (DTABR) values plotted for each electrode. Note the relatively highest values at ipsilateral, lateral frontal and anterior temporal electrodes. Note also that even the lowest DAR and DTABR values barely fall below 2.

Over the last decade, numerous studies have been published since this review demonstrating that quantitative (QEEG) measures of specific EEG features are likewise valuable in various clinical applications, including IS. In addition, compared with qualitative, visual analysis of EEG alone in (sub-)acute IS, QEEG methods have demonstrated improved detection and localisation capabilities, and QEEG-identified delta foci have been demonstrated to reliably correlate with lesion location on neuroimaging, including computed tomography (CT), positron-emission tomography (PET) or magnetic resonance imaging (MRI) (Nuwer et al., 1987; Nagata, 1989a; Murri et al., 1998; Luu et al., 2001; Fernandez-Bouzas et al., 2002; Finnigan et al., 2004; Sainio et al., 1983). EEG source analyses from a patient suffering anterior MCA IS (demonstrated on MRI), indicated that the scalp delta activity was generated by cortical regions within the MCA territory (in the lateral, anterior temporal and lateral frontal lobes; Finnigan et al., 2006). A recent case report of a left MCA patient reports similar EEG source localisation results (Phan et al., 2012; both studies employed the standardised, low-resolution electromagnetic tomography algorithm [sLORETA] for EEG source localisation analyses). However this review does not focus on QEEG-derived mapping or localisation applications *per se*, but on generalised or "global" QEEG measures.

A key QEEG metric salient to this review is power (signal intensity, with units microvolts squared) which is generally computed for EEG activity of specific frequencies (e.g., delta) using the fast Fourier transform (see Fig. 1). Tolonen and Sulg (1981) reported that such power measures had the strongest correlations with rCBF, relative to three alternative QEEG analysis methods.

"Bandpower" indices such as these do not encapsulate all of the complex information and features of the brain activity measured by EEG. However when computed and interpreted appropriately, QEEG measures can constitute effective indices of cerebral (dys)function which have clinical significance, as demonstrated below. Some clinical EEG systems now instantaneously compute and display such QEEG measures and trends in same (as well as standard EEG) and these are frequently considered in many hospitals in clinical management of neurological conditions such as neonatal hypoxic/ischaemic encephalopathy. In addition, emerging computer-assisted EEG interpretation systems have demonstrated potential to enhance non-expert identification of numerous EEG abnormalities in adult neurocritical patients (Cloostermans et al., 2011).

We will discuss those EEG features and QEEG measures that have demonstrated value for prognostication of post-stroke outcomes, and/or for monitoring stroke evolution, including in response to thrombolytic therapy. Unless otherwise stated, studies reviewed below used a standard, 19-electrode clinical EEG system.

2. QEEG monitoring and prognostication in acute and subacute ischaemic stroke

2.1. Studies using frequency-specific power measures

Firstly, some evidence from combined EEG and neuroimaging observations, as well as animal studies, suggests that alpha activity disturbances (e.g., amplitude attenuation; slowing) are generally indicative of cortical injury whereas abnormal delta activity reflects cortical deafferentation due to subcortical and/or white matter injury (e.g., Kaplan and Rossetti, 2011). However this is speculative and more evidence is required to definitively assess these possibilities. Of 20 QEEG measures computed using Fourier-derived or other analyses, delta power measures had the strongest correlation with rCBF (a negative correlation, and alpha power had a relatively strong positive correlation with the latter; Tolonen and Sulg, 1981). Other evidence indicates that delta activ-

Table 1
Summary of key details from studies reporting associations between early EEG/QEEG and outcome observations from ischaemic stroke.

Study	EEG time	Principal EEG/QEEG indices of prognostic value	Associated outcome assessment & time-point
Sainio et al. (1983)	<48 h	Delta power, alpha power	Neurological examination; Discharge
Cillessen et al. (1994)	1–10 d (median 3)	Delta activity, alpha and beta "background" activity (e.g., depression or asymmetry of background)	Modified Rankin scale; 12 months
Szelies et al. (2002)	2 weeks	Delta power, alpha power; Inter-hemispheric power asymmetries at fronto-temporal electrodes	Aphasia (Token test); 8 weeks
Cuspineda et al. (2003)	<72 h	Derivatives of power of delta, theta, alpha and beta; standardised relative to a normative database	Modified Rankin scale; 3 months
Finnigan et al. (2004)	<18 h	Global delta power, and acute changes in same	NIHSS; 30 days
Finnigan et al. (2007)	49 ± 3 h	Delta/alpha power ratio; relative alpha power	NIHSS; 30 days
Cuspineda et al. (2007)	<72 h	Delta power (standardised) Alpha and theta power (standardised)	Modified Rankin scale; 3 months Modified Rankin scale; Discharge
Burghaus et al. (2007)	<24 h (mean 15)	Slowed occipital alpha, or beta, activity; Focal delta (and sometimes also theta) activity	Neurological symptoms, CT (e.g., evidence of oedema, herniation, midline shift)
Tecchio et al. (2007)[a]	2–10 d (mean 5.2)	Delta power, particularly contralateral hemisphere	NIHSS; 7.8 months (median)
Zappasodi et al. (2007)[a]	2–10 d (mean 5)	Delta power & dipole strength (both hemispheres)	NIHSS (change); 9 months (median)
Finnigan et al. (2008)	<25 h	Delta power, particularly contralateral hemisphere	Death; 2–10 days
Leon-Carrion et al. (2009)	<1 week	Delta/alpha power ratio	Functional independence measure + functional assessment measure; 6 months
Sheorajpanday et al. (2010)	<72 h[b]	BSI DTABR	Radiologically-confirmed stroke, NIHSS deterioration or death; NIHSS improvement; <7 days
Sheorajpanday et al. (2011a)	<72 h[b]	BSI DTABR	Modified Rankin scale; disability; 6 months Modified Rankin scale; dependency, mortality; 6 months
Sheorajpanday et al. (2011b)	<72 h[b]	BSI DTABR	Radiologically-confirmed stroke; <96 h Modified Rankin scale; 7 days

DTABR: (delta + theta)/(alpha + beta) power ratio; BSI: brain symmetry index; NIHSS: national institutes of health stroke scale.
[a] Magnetoencephalographic data.
[b] 96 of 110 of patients had EEG in <72 h; the remainder in <7 days.

ity may reflect pathophysiological process(es) such as oxidative stress (Assenza et al., 2009; see below).

Key details from this section are summarised in Table 1. Initially Sainio et al. (1983) reported that in EEG recorded from 11 electrodes within 48 h of symptom onset in IS patients, high delta and/or low alpha power measures were the most reliable QEEG indicators of poor outcome assessed via neurological examination. In (sub-)acute IS patients, both qualitative and quantitative EEG observations were significantly more accurate in predicting 1-year functional outcomes than initial Rankin Scale (RS; Cillessen et al., 1994). Poor outcomes were predicted by delta activity and depression of faster alpha or beta activity in the ischaemic hemisphere, whereas good outcomes were predicted by absence of these phenomena. QEEG bandpower-derived measures in (sub-)acute IS, computed relative to a normative QEEG database, were reported to be significantly correlated with modified RS (modRS) at 3 months, and more so than was acute Canadian Neurological Scale (Cuspineda et al., 2003). Szelies et al. (2002) reported subacute QEEG power measures to be associated with degree of aphasia at 8 weeks. Interhemispheric power asymmetry scores, particularly for delta and alpha bands at lateral fronto–temporal electrodes, had significant associations with outcomes.

In the first reported investigations of serial EEG/QEEG in acute IS, it was noted that global delta (absolute) power often changed substantially over time, depending on stroke severity and evolution (Finnigan et al., 2004). In a sample containing both anterior and posterior circulation strokes a measure of the direction and mean hourly rate of such change correlated significantly with National Institutes of Health Stroke Scale (NIHSS) scores at 30 days (Finnigan et al., 2004). Importantly the QEEG-outcome correlation was stronger than or as strong as those between outcomes and acute diffusion or perfusion MRI measures, respectively. Similarly it has been reported that (sub-)acute IS delta power measures are valuable for predicting outcome NIHSS (median 7.8 months), and indeed these delta measures (acquired using magnetoencephalography [MEG]) enhanced the sensitivity and specificity of outcome prediction beyond those afforded by sub-acute perfusion MRI (Tecchio et al., 2007). Another study qualitatively classified EEG from (sub-)acute IS patients (mean 15 h post-stroke) according to five, frequency and topography criteria and compared these to stroke evolution assessed with neurological symptoms and CT (Burghaus et al., 2007). The EEG criteria predominantly related to observations described in the preceding paragraphs (e.g., presence of slow delta activity; slowing or attenuation of alpha activity). Patients with a malignant course (e.g., unilateral fixed, dilated pupil and midline shift) exhibited increased delta and diminished/slowed alpha, whereas benign strokes had an absence of delta and intact faster activity. These observations are consistent with others summarised above. In another acute IS study evolution of a contralateral delta power maximum indicated midline shift, was more prominent than parallel MRI changes, preceded NIHSS increases by >10 h, and prognosticated death (Finnigan et al., 2008).

Cuspineda et al. (2007) report (sub-)acute IS (<72 h) delta power to be the strongest and alpha the next best predictor of 3-month outcomes (modRS). In MEG data from subacute patients delta power (and other delta "amplitude" or current strength) measures were negatively correlated with clinical recovery (NIHSS change over median 9 months), and ipsilateral delta positively correlated with MRI lesion volume (Zappasodi et al., 2007). The same group reported that ipsilateral delta power was inversely correlated with plasma levels of transferrin, a glycoprotein which evidently limits oxidative damage in IS (Assenza et al., 2009). Significant correlations between QEEG indices at 48 h post-stroke and 30-day NIHSS have been reported. The strongest correlation (positive) involved delta/alpha power ratio (DAR), and indeed this was as strong as that between 48 h and outcome NIHSS scores (Finnigan et al., 2007). In addition 30-day NIHSS scores demonstrated a significant (negative) correlation with relative alpha power. DAR essentially quantifies the overall signal intensity of abnormal, slow delta activity, relative to that of (healthy) alpha activity (see Fig. 1). DAR was previously found to be the most effective of 12, frequency-specific indices in detecting delayed ischaemia, prior to symptom changes, in subarachnoid haemorrhage (Claassen et al., 2004). The (delta + theta)/(alpha + beta) power ratio (DTABR, sometimes alternatively termed the power ratio index) is obviously linked to DAR but is additionally sensitive to theta (4–7 Hz, typically) and beta activity, which may sometimes be informative to IS monitoring (Nuwer et al., 1987; Szelies et al., 2002; Machado et al., 2004; Burghaus et al., 2007). We also observed correlations between sub-acute DTABR (as well as relative delta power) and outcomes, which did not maintain significance following statistical correction (Finnigan et al., 2007). In (sub-)acute IS (and TBI) patients DAR, but neither DTABR nor a brain symmetry index, significantly correlated with 6-month functional outcomes (Leon-Carrion et al., 2009). Global power ratio indices such as these – which are computed from absolute bandpower measures – constitute single numerical values which are relatively straightforward to interpret. For example, at a very general level it may be appropriate to consider a global DAR or DTABR value of approximately one or less to be within a relatively normative range but values higher than approximately two, abnormal (see Fig. 1D). These power and ratio measures are typically computed from unipolar channels (e.g., referenced to vertex, averaged mastoids, or common average) although supplementary data analyses indicate they may be similarly informative if computed from bipolar channels.

2.2. Studies using the brain symmetry index (BSI)

The BSI provides a generalised measure of left–right EEG power (a)symmetry, by quantifying the difference in mean spectral power per hemisphere across 1–25 Hz (thus not specific to individual frequency bands; van Putten et al., 2004; van Putten, 2007). In stroke studies the BSI has generally been computed from four bipolar channels per hemisphere. The BSI also is a simple numerical value, ranging between zero (perfect symmetry for all channels) and one (maximal asymmetry), whereby the latter clearly is highly abnormal. An illustration of the BSI in quantifying abnormal hemispheric asymmetry is shown in Fig. 2. BSI was found to correlate with concomitant NIHSS in acute IS (van Putten and Tavy, 2004) and in subacute IS, with admission NIHSS and DWI lesion volume (Sheorajpanday et al., 2009). In the latter study the "pairwise-derived" BSI (pdBSI) was used, whereby pairwise indicates that (a)symmetry along homologous, interhemispheric channel pairs (e.g., F3-C3 versus F4-C4) is assessed, rather than global (a)symmetry. Across 110 (sub-)acute IS patients of varying Oxford Community Stroke Project (OCSP) ischaemia classifications (anterior, posterior, lacunar) DTABR was significantly correlated with 6-month outcomes (modRS), as was pdBSI (Sheorajpanday et al., 2011a). DTABR was a strong independent predictor of dependency and mortality, and pdBSI, of disability. Apart from these indices only acute/subacute NIHSS was an independent (weaker) predictor of these outcomes. In this large sample the median DTABR and BSI values were 4.4 and 0.18 respectively, while median NIHSS score was 6. In acute anterior circulation syndrome (ACS) of presumed ischemic origin patients with NIHSS score of 0 or 1, pdBSI was an independent predictor for definite stroke, early neurological deterioration or death; whereas spontaneous neurological improvement was independently predicted by DTABR (Sheorajpanday et al., 2010). In patients with lacunar (LACS) or posterior circulation (POCS) syndrome of presumed ischaemic origin, pdBSI emerged as a independent predictor for definite stroke (confirmed radiologi-

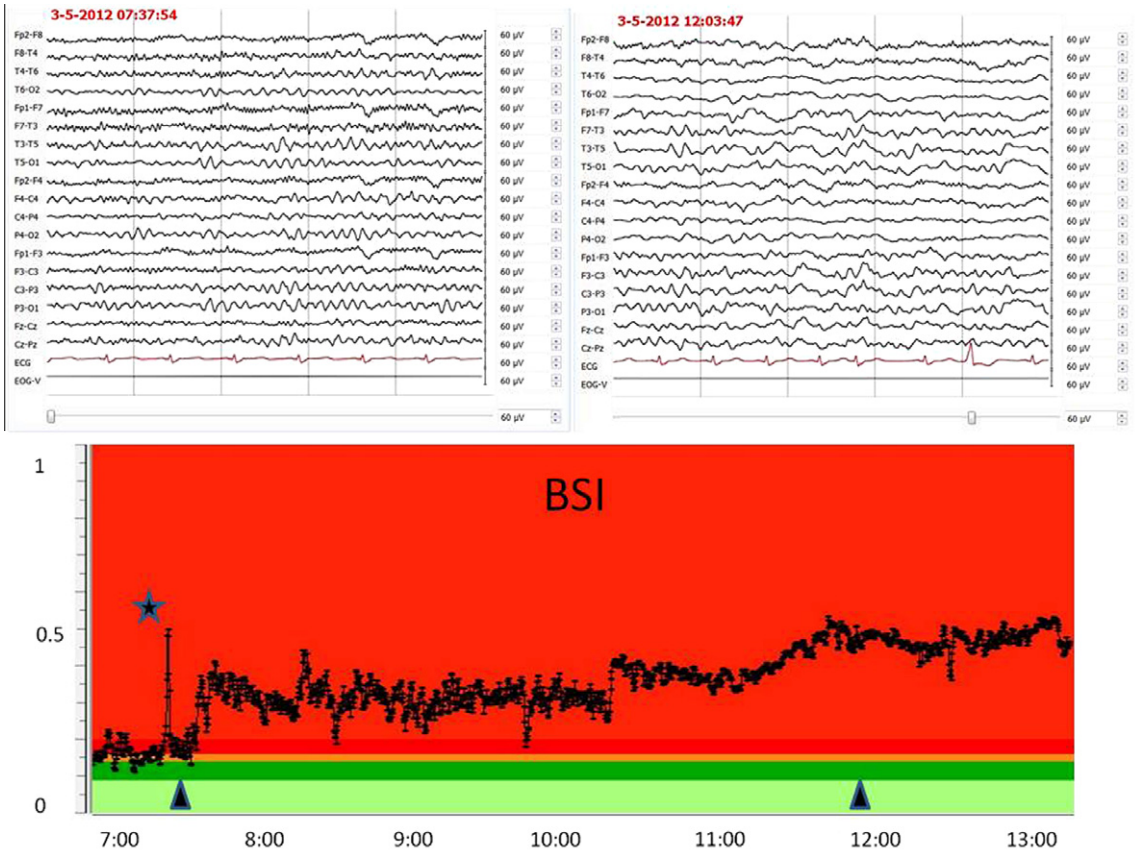

Fig. 2. Two EEG epochs acquired from a patient during carotid endarterectomy are shown. Initially, the EEG is nearly symmetrical (top left panel), but during the procedure a significant asymmetry develops, with disappearance of theta/alpha activity over the right hemisphere, showing mainly low-voltage polymorphic delta waves. The left hemisphere shows some generalised slowing too, intermixed with delta activity (top right panel). The top left and top right panels correspond to the times indicated in the bottom panel by the triangles at bottom left and right, respectively. First, the brain symmetry index (BSI) shows a slightly increased value (BSI ~0.15), with a significant increase to BSI ~ 0.5. Post-operation this patient suffered from a left-sided hemiplegia, that fortunately improved, with a residual moderate paresis of her left arm. The cause was most likely a severe drop in blood pressure during the procedure, shortly after anaesthesia. The asterisk indicates an artefact.

cally) even in patients with a NIHSS score of 0 (Sheorajpanday et al., 2011b). In LACS the DTABR correlated with lesion volume and predicted unfavourable outcome (modRS) at day 7. Other indices (e.g., DAR) were not reported in these studies so their predictive values cannot be compared.

2.3. Interim summary and proposal

The numerous outcomes reviewed above provide substantial evidence to support refutation of two proposals in a past review (Faught, 1999). Firstly it is now evident that in various circumstances EEG/QEEG has substantial (and more than "questionable") value in addressing the question, "Is this stroke getting better or worse?". This particularly applies to continuous or serial EEG/QEEG assessments over time-frames of some hours or longer. For example, reductions in delta power, DAR, DTABR or BSI during the acute IS interval are generally associated with relatively better functional outcomes. On the other hand, increases in these measures or emergence of a contralateral delta focus in acute IS indicates worsening cerebral pathophysiology and an unfavourable prognosis. Moreover, following thrombolysis significant delta reductions or BSI changes have been observed over scales of minutes (see next Section). Importantly, such QEEG changes over time have repeatedly been observed well before marked changes in patients' neurological symptoms. In cases when repeat MRI has been performed over similar timeframes the prognostically-salient QEEG changes have occurred in the absence of parallel changes on diffusion-weighted MRI (Finnigan et al., 2004, 2006, 2008). In addition numerous studies reviewed above report converging observations which collectively indicate that QEEG indices in (sub-)acute IS generally are strongly associated with functional outcomes at up to 12 months post-stroke**.** Acute/subacute QEEG has generally demonstrated greater prognostic efficacy than concomitant clinical scales and if anything improved upon the prognostic ability afforded by neuroimaging alone. These outcomes clearly attest that the proposal that EEG cannot answer or uniquely inform the question, "What is the prognosis?" (Faught, 1999) also can now be refuted. This revised position is consistent with others (e.g., Jordan, 2004; Niedermeyer, 2003; Sheorajpanday et al., 2011a).

3. Monitoring treatment: QEEG during thrombolysis

EEG/QEEG is feasible for continuous bedside monitoring whereas neuroimaging modalities such as CT or MRI are not. A potentially promising future clinical application of continuous EEG/QEEG in acute IS could be in the immediate, bedside monitoring of response to thrombolytic therapy (see Fig. 3). A rapid, significant reduction in global delta power was observed within 25 min following commencement of intravenous tissue plasminogen activator (i.v. tPA), and preceding symptomatic changes by almost 2 h (Finnigan et al., 2006). EEG source localisation analyses computed using and compared to MRI indicated that the pre-treatment delta was generated by ischaemic cortical tissue which was reperfused post-thrombolysis (Finnigan et al., 2006). We have observed analogous, prompt delta power reductions in several tPA recipients (e.g., Finnigan et al., 2004, 2007). These were consistently observed

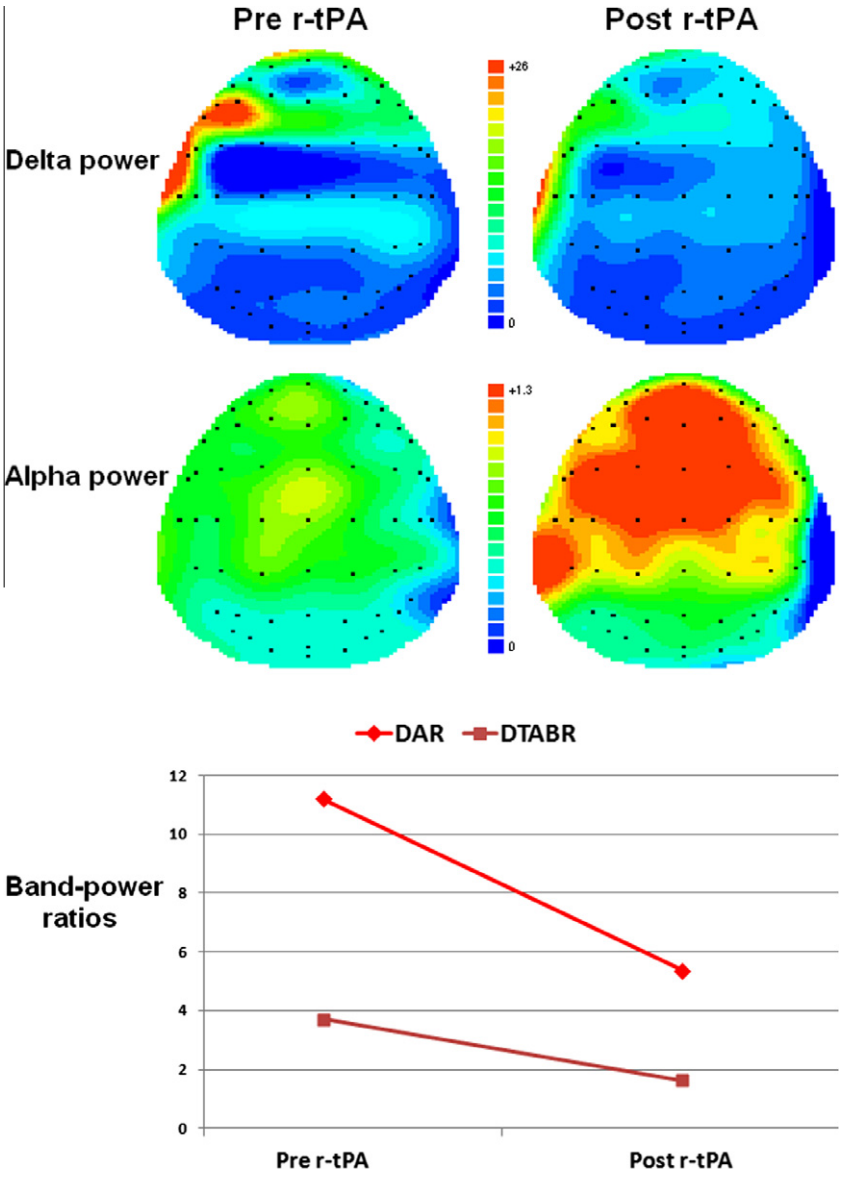

Fig. 3. Illustrating significant changes in the EEG, and QEEG measures, between pre versus post, recombinant tissue plasminogen activator (r-tPA). These EEG data were acquired from a 67-year old male at approximately 5.5 (left) and 7.5 h (right) after onset of symptoms associated with ischaemic stroke in the left middle cerebral artery territory. The NIHSS score was 21 immediately prior to EEG. Maps illustrate the scalp topography of mean delta (top) and alpha (middle) power. Corresponding, global delta/alpha ratio (DAR) and (delta + theta)/(alpha + beta) power ratio (DTABR) values are plotted (bottom). Intravenous r-tPA administration commenced within 6 h as part of a randomised double blind controlled trial. Note the initial ipsilateral, fronto-temporal delta power focus (top left). Comparing pre to post r-tPA, also note reduced delta power at these and adjacent electrodes and increased alpha power at many electrodes, as well as the dramatic drop in the DAR (averaged across all electrodes). As described in the text, we have observed such post r-tPA QEEG changes over scales of tens of minutes and well before any substantial symptom changes. Note the differential power scales for delta versus alpha.

within tens of minutes of injection (at most) and preceding substantial symptomatic changes by similar or greater time-frames. Reporting these outcomes is currently in progress. In serial EEG from 16 tPA recipients a significant correlation was reported between changes in the BSI, and NIHSS changes (de Vos et al., 2008). These changes were generally reported over approximately several hours, in one case over less than an hour. In another exemplar case BSI dropped post-thrombolysis over a brief time-frame similar to that reported in our aforementioned study. Unfortunately this study did not report additional data from intermediate time-points, hence the respective temporal resolutions of (perhaps prompter) BSI changes versus (subsequent) clinical changes were not assessed in detail. In all but two of 16 patients the BSI was observed to change over a period of (median 5.8) hours in the acute IS interval, similar to previously-reported delta power changes according to acute IS evolution (Finnigan et al., 2004). A recent case study reports pre-tPA delta activity with a left fronto–temporal maximum at 3.5 h after onset of left middle cerebral artery IS (Phan et al., 2012). The patient made a dramatic clinical recovery and complete recanalisation was confirmed by MR angiography. The authors report resolution of delta activity by 48 h post-stroke, but unfortunately did not report any EEG observations which may have been made soon after tPA administration.

4. Practical considerations, potential limitations and complementary techniques

This review does not focus upon specific investigations of seizure activity in IS, although such observations are reported elsewhere (e.g., Jordan, 2004; Mecarelli et al., 2011). EEG obviously

is imperative for monitoring (non-convulsive) seizure activity in various conditions and recent evidence indicates that computer assisted EEG (or indeed QEEG) monitoring may improve early detection of seizure activity (as well as other abnormalities, e.g., slowing) in stroke and other neurocritical patients (Cloostermans et al., 2011).

Caveats to the use and interpretation of EEG/QEEG data, for example in relation to artefacts and sleep/wake states have been discussed. For example the possibilities that delta measures may be contaminated by sleep/drowsiness, medications or eye movements have been addressed (e.g., Diedler et al., 2009; Finnigan et al., 2004, 2007). Effective identification and exclusion or correction of artefacts remains a challenge (e.g., Cloostermans et al., 2011) as it does for other modalities including neuroimaging. However significant advances on this front have been achieved via computational approaches such as those implemented in freely available EEG analysis software tools (Delorme et al., 2011). With regard to low-frequency delta activity in particular, probably the key form of artefacts of concern are those associated with eye blinks or movements. In some but not all cases, asking patients to attempt to minimise the regularity of these can be useful. Eyes-closed recordings generally obviate blinks as an issue. However in our experience (e.g. Finnigan et al., 2007), in some cases such artefacts are still obtained and the potential confounding impact of these on QEEG measures of interest can be minimised by an appropriate correction procedure such as that of Semlitsch et al. (1986). Such algorithms are implemented into numerous EEG analysis software packages, and can be informed either by appropriately-positioned electro-oculogram (EOG) electrodes or alternatively, electrodes FP1 and FP2 of the international 10–20 system. In addition, in a study monitoring acute hemispheric IS patients during thrombolysis, the BSI was based on a montage of four bipolar channels per hemisphere (F3-C3, C3-P3, P3-O1, T5-O1, F4-C4, C4-P4, P4-O2, T6-O2; de Vos et al., 2008). In order to minimise possible contamination of BSI measures by potential artefacts associated with eye blinks or movements and electromyogram (EMG) from temporal muscles, frontopolar and temporal electrodes were not included in this montage.

There will be cases wherein EEG/QEEG may not add significant and novel information to guide management, or in which no treatment/management options are available which may otherwise be informed by EEG/QEEG. Scalp EEG may not always reliably assess pathophysiology in focal, subcortical lesions (Jordan, 2004) although the findings of recent large studies suggest that EEG/QEEG monitoring is useful in all IS types regardless of localisation and OCPS classification (Sheorajpanday et al., 2011a,b). Other outcomes also indicate QEEG is useful in subcortical strokes (Murri et al., 1998; Nagata et al., 1989b; Szelies et al., 2002). Less has been reported about the value of QEEG in haemorrhagic stroke although some evidence (Claassen et al., 2004; Fernandez-Bouzas et al., 2002; Rathakrishnan et al., 2011) indicates that the outcomes reviewed above may be generally applicable. Future research can further investigate these topics.

EEG/QEEG cannot replace neuroimaging techniques such as MRI or CT. Such modalities often are complementary and collectively deliver more comprehensive assessments than either in isolation (Jordan, 2004; Finnigan et al., 2004). At the same time, diffusion-weighted MRI is not abnormal in all patients with IS: reported values for the sensitivity range from 80% to 90% (Schellinger et al., 2010; Doubal et al., 2011). Presumably, in some patients with IS neuronal death does not occur, whereas the cause of the neurological deficits may result from permanently compromised synaptic function (Bolay et al., 2002; Hofmeijer and van Putten, 2012). Much is known about the pathophysiology of ischaemia at the biochemical, synaptic and cellular levels of analysis (e.g., Brouns and De Deyn, 2009; Dirnagl et al., 1999; Hofmeijer and van Putten, 2012). However as noted above it remains unresolved as to precisely what pathophysiological mechanism(s) are manifest in EEG as delta activity, or alpha slowing or attenuation, or other patterns. As a hypothetical example: does delta activity possibly index pathophysiology of the infarct core (perhaps exitotoxicity or oxidative stress) or alpha attenuation, that of the ischaemic penumbra? (cf. Machado et al., 2004). Evidently, more plausible is the position that slow (delta, theta) activity is generated by the penumbra (e.g., see Finnigan et al., 2004, 2006; Hofmeijer and van Putten, 2012; Jordan, 2004; Phan et al., 2012). Further investigation of these salient issues also should carefully consider the adverse effects of cerebral ischaemia on various aspects of synaptic function (cf. Hofmeijer and van Putten, 2012). The answers are likely not straightforward yet resolution of such questions is an important, albeit challenging, objective; progress towards which should help promote broader understanding and translation of QEEG indices and findings such as those reviewed above. Such progress will surely require not only basic neuroscience studies in animal models but also clinical, multi-modality neuroimaging investigations, likely involving EEG as well as perfusion CT (e.g., Bivard et al., 2011) and perhaps other methods.

As brain network connectivity is generally altered after stroke, techniques that quantify properties of neural network architecture or functional connectivity have been applied to study changes in same during stroke recovery. Although most studies have used functional MRI (e.g., Grefkes and Fink, 2011; Wang et al., 2010) evaluation of network reorganisation after stroke using EEG techniques has also been reported, for example with the aim of investigating reorganisation in contralesional motor areas (Gerloff et al., 2006). In another study, graph theoretical measures from EEG data were used to investigate functional connectivity during preparation and execution of a finger-tapping task in subcortical stroke patients, demonstrating a reduced capacity to integrate information between distant brain regions (De Vico et al., 2009). Such analysis methods may inform future assessments of post-stroke recovery, perhaps in response to rehabilitative interventions.

5. Outlook and future applications

EEG is widely available, relatively inexpensive, non-invasive and virtually free of contraindications. As outlined in more detail below, two key applications of QEEG which should prove valuable for future clinical management of IS are: (1) continuous, acute monitoring to inform about the efficacy of thrombolysis and decisions about intra-arterial intervention, and (2) brief, subacute recording to inform outcome prognostication and decisions about, for example, rehabilitation strategies.

Among the most prognostically-salient measures have been those sensitive to the power of delta activity, relative to faster activity: the DAR (Claassen et al., 2004; Finnigan et al., 2007; Leon-Carrion et al., 2009), DTABR (Sheorajpanday et al., 2011a) or relative delta power (e.g., Claassen et al., 2004; Finnigan et al., 2007). Other studies did not analyse such power ratios but their outcomes suggest that DAR may be optimal for prognoses (Burghaus et al., 2007; Cuspineda et al., 2007; Nuwer et al., 1987; Szelies et al., 2002). Of course DAR and DTABR are not independent measures (e.g., see Fig. 1D), although the only studies which have compared DAR and DTABR within samples have reported DAR to have substantially stronger correlations with outcomes (Finnigan et al., 2007; Leon-Carrion et al., 2009). Such outcomes are consistent with indications that theta and beta activity do not provide as reliable measures of post-stroke pathophysiology as do delta and alpha (Finnigan et al., 2007; Nuwer et al., 1987; Sainio et al., 1983; Tolonen and Sulg, 1981). Relative delta and alpha power measures may also supplement DAR or DTABR in the assessment of post-IS

cerebral pathophysiology (Finnigan et al., 2007). As summarised above the "broadband" BSI also has demonstrated significant prognostic utility. Reduction in asymmetry driven by ipsilateral–contralateral shift of a delta focus may potentially appear anomalous or be misinterpreted by non-experts as prognostically favourable (Finnigan et al., 2007, 2008). This and other observations (Sheorajpanday et al., 2011a,b) suggest that investigation of both bandpower- and symmetry-related QEEG indices is optimal for outcome prognostication. Future studies well may demonstrate that an index sensitive to both is most effective. Indeed one study reported that bandpower-specific (particularly delta, and alpha) asymmetry measures most effectively prognosticated aphasia outcomes (Szelies et al., 2002). As noted above one apparently beneficial feature of both DAR/DTABR and BSI is they each constitute a single numerical value. Likewise relative bandpower measures are expressed as percentages. These features render such QEEG indices relatively readily-interpretable by non-specialist clinical staff, for example as "degree of generalised abnormality" measures. In addition it has been proposed that identification of normative ranges or criterion value(s) for healthy versus abnormal QEEG measures may advance clinical translation and utility (Finnigan et al., 2007). Sheorajpanday et al. (2011b) posit that pdBSI <0.12 delivered 100% specificity for the absence of a recent ischaemic lesion in 110 ACS, POCS and LACS patients, while DTABR <1 was 100% specific for the absence, and >3.5 was 100% sensitive for the presence, of such a lesion. Future investigations should build upon these promising observations.

Observations reviewed above further suggest that EEG/QEEG may uniquely inform acute clinical management of IS. Although further investigation is required in larger samples, these few studies provide preliminary evidence that continuous EEG/QEEG monitoring during thrombolysis could provide real-time information about the efficacy of i.v. tPA, prior to potential clinical changes. Such observations may in turn uniquely inform future decisions for example in "bridging" trial protocols wherein intra-arterial therapy (with tPA and/or a thrombectomy device) is administered if i.v. tPA is deemed unsuccessful within a predetermined time window (Donnan et al., 2011). Irrespective of intra-arterial therapy, continuous monitoring during and after i.v. tPA may enable earlier identification of relatively successful (e.g., "rapid neurological recovery after i.v. tPA": NIHSS score improvement of at least 50% within 24 h; Machumpurath et al., 2011) versus unsuccessful recanalisation, each of which should have distinct clinical management implications. In addition these and other outcomes (e.g., Finnigan et al., 2004) indicate that continuous EEG/QEEG may also prove uniquely informative for identifying resolution of cerebral ischaemia, such as in transient ischaemic attacks, prior to symptomatic improvement. These potential applications should be productive foci for future studies.

Transcranial Doppler ultrasound (TCD-US) has been used to monitor recanalisation during thrombolysis and there is evidence that concomitant US may enhance the efficacy of same (Donnan et al., 2011; Molina and Alexandrov, 2007). The TCD-US monitoring technique is not without its own technical difficulties (albeit neither is EEG). It would be interesting and potentially rewarding to prospectively investigate the usage of both EEG and TCD-US during thrombolysis and to compare the respective efficacies of the two techniques (and perhaps a multi-modality index which integrates the two) particularly for monitoring during and after thrombolysis.

Ongoing availability of EEG hardware and technical expertise can be a challenge particularly for on-call or continuous monitoring, but not insurmountable. Across the studies reviewed herein there has been substantial variability in the time of EEG (post-stroke onset; see Table 1). Some studies have acquired EEG within several hours (e.g., Finnigan et al., 2004, 2006; de Vos et al., 2008), some at several or more days post-stroke and others, at one or another time across this range within the same sample (e.g., Cuspineda et al., 2003; Sheorajpanday et al., 2011a). Clearly, EEG monitoring during thrombolysis must by definition occur within several hours of stroke onset. However for the other proposed application of QEEG in ischaemic stroke – informing outcome prognostication – an important question is: what is the optimal time to perform EEG? Sheorajpanday et al. (2011a) compared the prognostic value of QEEG (DTABR and pdBSI) between two distinct subsamples of patients: those with EEG acquired within 24 h ($N = 72$) and those with EEG acquired within 24–72 h ($N = 24$). For both QEEG indices analysed the latter, subacute EEG sample demonstrated higher correlations with NIHSS at 7 days, modRS at 6 months, and also with infarct volume (on follow-up MRI). These and consistent outcomes (Finnigan et al., 2004, 2007) indicate that – apart from cases of acute thrombolysis or other interventions – QEEG may more reliably inform outcome prognostication when acquired in the subacute period. This topic warrants further investigation however numerous studies' outcomes indicate that QEEG measure(s) from a single, brief recording within or at approximately 72 h of stroke onset can uniquely inform clinical prognoses and management.

The available data also indicate that a high-density electrode array is not essential and a standard clinical EEG array, which is more feasible for routine usage, generally is adequate for post-stroke monitoring and prognoses. Indeed many BSI studies have used only eight electrodes. Previously we used a 64-channel system but demonstrated that this doesn't necessarily provide significantly more useful information than the standard clinical methodology (Finnigan et al., 2007, 2008). For MCA strokes at least, even fewer, specifically-positioned electrodes may prove similarly effective (e.g., Finnigan et al., 2004, 2007, 2008; Szelies et al., 2002) and perhaps provide even more specific measures (Sainio et al., 1983). Indeed we have observed that in a sub-sample of ten patients suffering IS in the MCA territory (reported in Finnigan et al., 2007), subacute DAR (as well as relative delta and alpha power) measures maintain significant correlations with 30-day NIHSS scores even when computed and averaged from only four frontal electrodes (F3, F4, F7, F8; referenced to Cz). These are important considerations because acquiring a brief, standard (or perhaps even "lower-density") EEG in the subacute period clearly is more feasible than, for example, a continuous, high-density montage recording commencing prior to thrombolysis and continuing for hours.

A recent report authored by many global opinion leaders in stroke medicine proposes a number of recommendations aiming to reduce the risks, effects and consequences of stroke. One such recommendation is the identification of surrogate assessments, and physiological markers, which can be "used as predictive tools for outcome and thus be of value for triage; as entry criteria in clinical trials of repair-related therapies; or in evaluating treatment outcomes to guide clinical decision-making" (Hachinski et al., 2010). On the basis of outcomes and evidence reviewed above it appears that QEEG indices such as DAR/DTABR and BSI likely constitute effective physiological markers for such future clinical applications. Future studies can further investigate the value of such QEEG indices including in relation to assessment of post-stroke recovery and perhaps the efficacy of one or another intervention.

Some contemporary clinical EEG systems automatically compute and display cross-temporal trends in QEEG indices such as those reviewed above, so at least visual inspection of these at the bedside is achievable. Moreover recent investigations in stroke and other adult neurological ICU patients indicate that emergent, computer-assisted EEG/QEEG monitoring systems can accurately interpret numerous common EEG abnormalities, and thereby facilitate initial recognition of same by non-expert clinical staff (Cloostermans et al., 2011). Further advancement of research,

knowledge and technologies in this field over the coming years should facilitate increasing translation of QEEG, as well as delivering novel insights into evolving cerebral pathophysiology in stroke and other neurocritical patients. These in turn should enhance clinical management and help realise improved outcomes for such patients.

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