

- Fuglsang-Frederiksen A. Diagnostic criteria for amyotrophic lateral sclerosis. *Clin Neurophysiol* 2008;119:495–6.
- Kleine BU, Schelhaas HJ, Stegeman DF, Zwarts MJ. A prospective, blind study of the triple stimulation technique in the diagnosis of ALS. In: *Proceedings of IXth quantitative EMG conference*, 3–6 June 2007, Ljubljana, Slovenia, p. 163.
- Kleine BU, Stegeman DF, Schelhaas HJ, Zwarts MJ. Firing pattern of fasciculations in amyotrophic lateral sclerosis: evidence for axonal and neuronal origin. *Neurology* 2008;70:353–9.
- Knottnerus JA, van Weel C, Muris JWM. Evidence base of clinical diagnosis. Evaluation of diagnostic procedures. *BMJ* 2002;324:477–80.

H.J. Schelhaas
Department of Neurology,
Radboud University Nijmegen Medical Center,
Reinier Postlaan 4, P.O. Box 9101,
6500 HB Nijmegen, The Netherlands
Clinical Neurophysiology,
Radboud University Nijmegen Medical Center,
The Netherlands
Netherlands ALS Centre,
The Netherlands
E-mail address: H.schelhaas@neuro.umcn.nl

B.U. Kleine
 M.J. Zwarts
Clinical Neurophysiology,
Radboud University Nijmegen Medical Center,
The Netherlands

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Contralateral hemisphere delta EEG in acute stroke precedes worsening of symptoms and death

A number of recent studies report that quantitative electroencephalography (QEEG) measures of cerebral pathophysiology in acute or sub-acute stroke might augment future prognoses regarding patient outcomes (e.g., Claassen et al., 2004; Cuspideda et al., 2003; Finnigan et al., 2004, 2006, 2007; Jordan, 2004; Tecchio et al., 2007; van Putten and Tavy, 2004; Zappasodi et al., 2007). For example we have reported that QEEG delta (~1 to 4 Hz) power measures in acute stroke (Finnigan et al., 2004, 2006) and delta/alpha power ratio (DAR) measures in sub-acute stroke (Finnigan et al., 2007) are both highly correlated with ischaemic stroke patients' outcomes assessed via the National Institutes of Health Stroke Scale (NIHSS). QEEG measures were averaged over all scalp electrodes and further a significant correlation between subacute DAR and outcome measures was obtained when the former was computed from a standard, 19-electrode array. Some QEEG measures incorporate separate computations for each cerebral hemisphere (e.g. van Putten and Tavy, 2004); Tecchio et al. (2007) acquired hemisphere-specific

magnetoencephalography (MEG) data from subacute ischaemic stroke patients and reported that delta measures from the contralateral hemisphere (CH) appear valuable in predicting clinical outcome assessed via NIHSS at follow-up (median 7.8 months post-stroke). Moreover, multinomial logistic regression analyses revealed that this QEEG measure *per se* enhanced the sensitivity and specificity of outcome prediction beyond that afforded by subacute lesion volume defined via perfusion-weighted magnetic resonance imaging (MRI). These outcomes are consistent with QEEG and other observations we have acquired from acute ischaemic stroke patients, including those who have deceased in the ensuing days. Here we report cross-temporal NIHSS, QEEG and MRI data from two such patients. Approval to carry out the study was obtained from the local University and Hospital Human Experimental Ethics committees, and informed consent was obtained from the patients' spouses.

The first patient (patient A), a 82-year-old woman, presented with symptoms including left-sided hemiplegia, minor left facial paralysis, a complete left hemianopia, severe left-sided sensory loss, forced gaze deviation to the right, right leg motor drift, complete left-sided neglect and drowsiness. The NIHSS score was 22 when assessed at 6 h after symptom onset (hereafter termed "post-stroke"). The Glasgow Coma Score (GCS) was 13 when assessed at several times within the first 24 h post-stroke. Structural and diffusion-weighted MRI (DWI) data were acquired at 6 h, 15 min and again at 18 h, 30 min post-stroke. Resting EEG data were acquired at the bedside for 20 min per recording, at 8 h, 20 min post-stroke as well as at 17 h, 15 min and 25 h, 25 min post-stroke. Patient inclusion/exclusion criteria as well as additional MRI and EEG data acquisition and analysis methods followed those previously reported by ourselves (e.g., Finnigan et al., 2004). As illustrated in Fig. 1 the DWI scans demonstrated a large abnormality in the middle cerebral artery (MCA) and anterior cerebral artery (ACA) territories of the right hemisphere. The initial EEG data (acquired at 8 h, 20 min post-stroke) demonstrated pronounced delta oscillations which were of highest mean power at right, fronto-central and fronto-temporal electrodes. Nine hours later, delta power remained similarly high only at those fronto-temporal sites, as well as at frontal electrodes over the left (contralateral; CH) hemisphere. A further 8 h later at 25 h, 25 min post-stroke, mean delta power was highest not at right hemisphere (ipsilateral; IH) sites but at left (CH) frontal, fronto-central and fronto-temporal electrodes. Across 16 h during the acute stroke period, the scalp topography of high-voltage delta oscillations evolved from IH to CH maxima. In contrast to these pronounced QEEG changes, during the first half of this time-frame the NIHSS score improved from 22 to 20 and then remained unchanged across the subsequent 8 h.

The NIHSS score at 48 h post-stroke had increased to 23. This increase reflected increased severity of facial paralysis, emergence of right arm motor drift and ataxia.

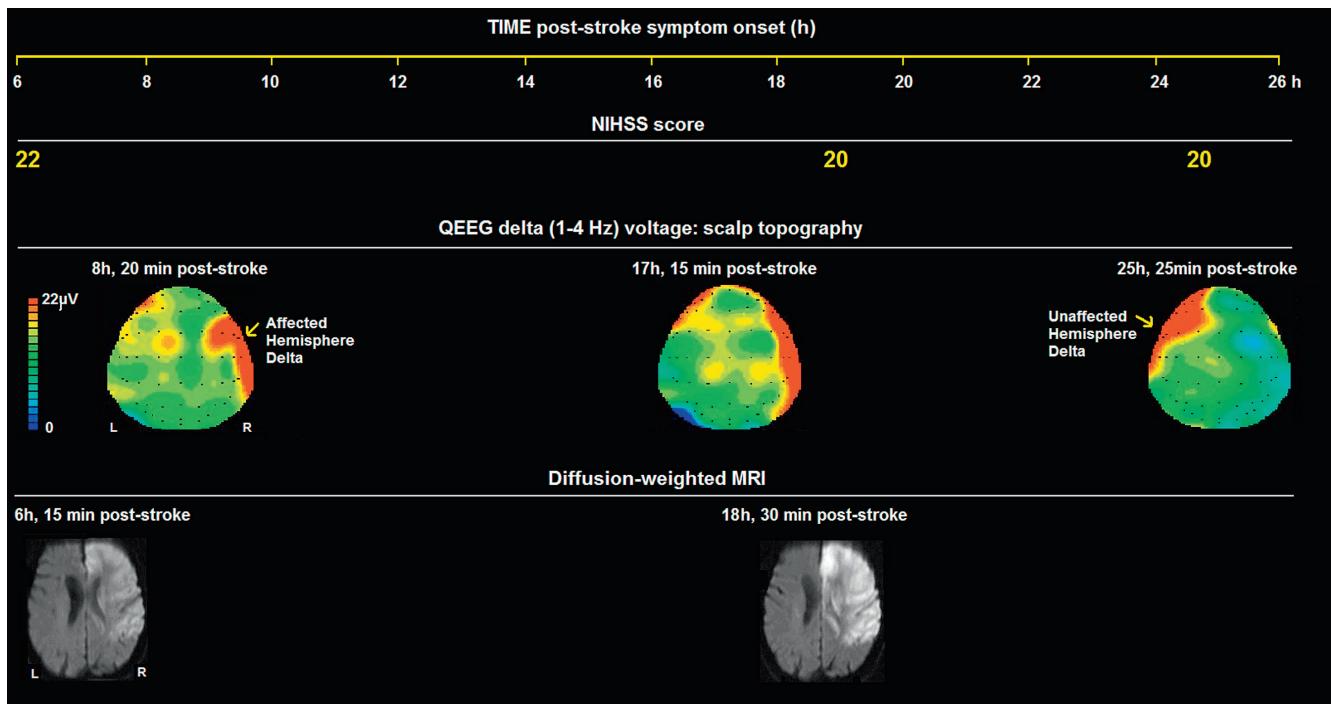


Fig. 1. NIHSS, QEEG delta scalp topography maps, and DWI scans acquired from patient A at several time-points during the acute post-stroke period. Note that orientation of MRI scans is reversed from radiological format to facilitate direct comparison with QEEG maps.

This patient was thereafter withdrawn from the research study and subsequent NIHSS, EEG and MRI observations were not made. Relative to the GCS of 13 during the first 24 h post-stroke, this did not substantially change over the ensuing 48 h and was 14 at two days post-stroke. However the GCS was 6 at four days, and 4 at eight days post-stroke. The patient died at 10 days post-stroke after a progressive deterioration, in the absence of any further, emergent neurological symptoms which – had those occurred – might have reflected, for example, the event of an additional stroke in one or another hemisphere. Moreover no other obvious accelerating factor, such as infection or pulmonary embolus, became apparent during this period. Hence all available observations indicate that this patient's death was a direct consequence of the stroke which occurred prior to the observations reported herein; albeit further (e.g. EEG, MRI) observations which could have definitively confirmed this were not obtained in the days immediately preceding death, for reasons noted above. Nevertheless, of the acute NIHSS, QEEG and DWI observations, the significant topographical changes in delta power over time – i.e., the shift from IH to CH maxima – proved to be the most salient with regard to prognosis.

The second patient (patient B), a 86-year-old woman, presented with symptoms including right-sided hemiplegia, right-sided complete facial paralysis, left arm motor drift, left leg paralysis, bilateral hemianopia, total gaze paresis with eyes deviated to the left, muteness, severe dysarthria, complete right-sided neglect, and drowsiness. The NIHSS score was 33 when assessed within 4 h of

symptom onset. A computed tomography (CT) head examination indicated oedema in the frontal, temporal and parietal lobes of the left hemisphere, consistent with large, left MCA stroke. Structural and diffusion-weighted MRI (DWI) data were acquired at 4 h, 40 min and again at 15 h, 20 min post-stroke. Resting EEG data were acquired at the bedside for 20 min per recording, at 6 h, 15 min post-stroke as well as at 10 h, 10 min and 14 h, 20 min post-stroke. As illustrated in Fig. 2 the DWI scans demonstrated a large abnormality in the left MCA territory as well as much of the left ACA territory. It is noteworthy that in the first scan there appears to also be a minimal DWI abnormality deep in the right hemisphere (CH). The second DWI scan (at 15 h, 20 min post-stroke) shows that the DWI abnormality had spread into medial regions of the left ACA territory and in addition the small CH abnormality was more evident. We have not previously observed the latter DWI phenomenon in other stroke patients whom we have studied, and the possible relationship between this and CH delta would be an interesting topic of investigation for future studies in larger patient samples. In the present data however, high-voltage CH delta activity was evident 9 h prior to this DWI observation; the initial EEG data at 6 h, 15 min post-stroke demonstrated pronounced delta oscillations which were of highest mean power at frontal electrodes over both hemispheres (see Figs. 2 and 3). Four hours later, delta power was clearly highest at a number of electrodes overlying the right hemisphere (CH), particularly frontal and central sites. A similar QEEG delta scalp topography was observed a further

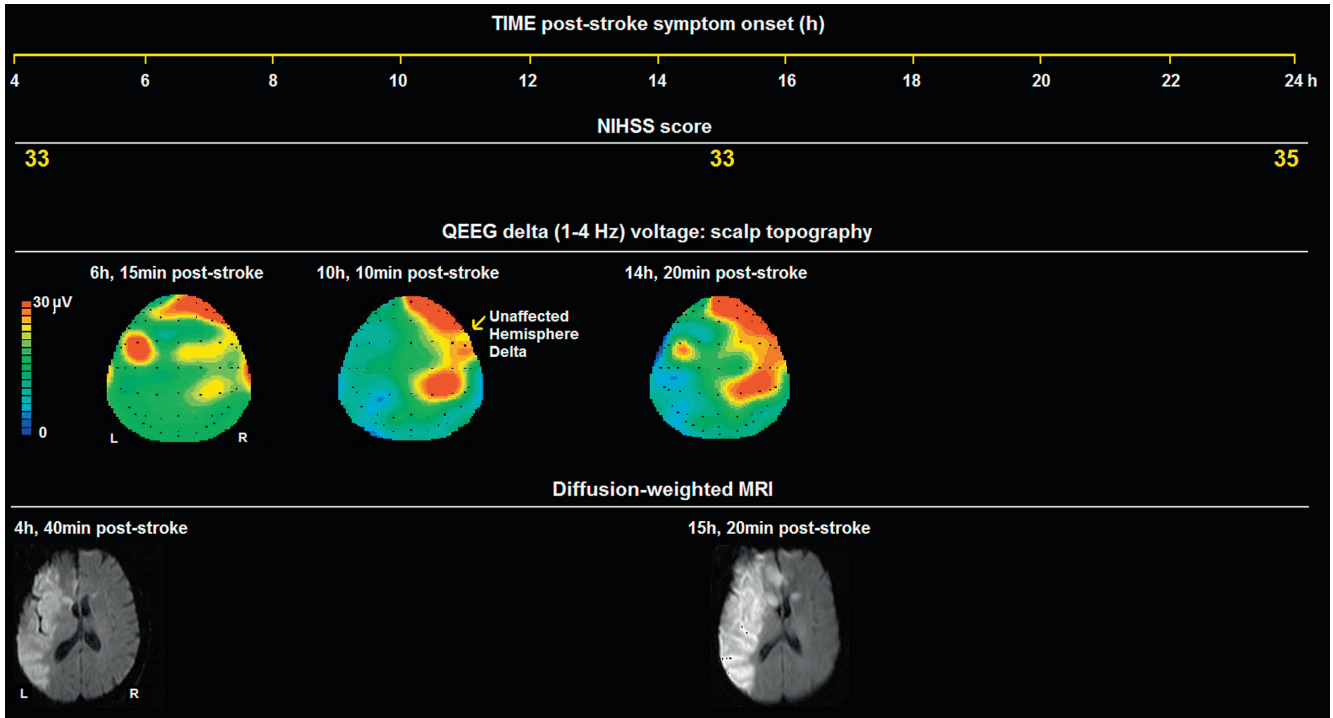


Fig. 2. NIHSS, QEEG delta scalp topography maps, and DWI scans acquired from patient B at several time-points during the acute post-stroke period. Note that orientation of MRI scans is reversed from radiological format to facilitate direct comparison with QEEG maps.

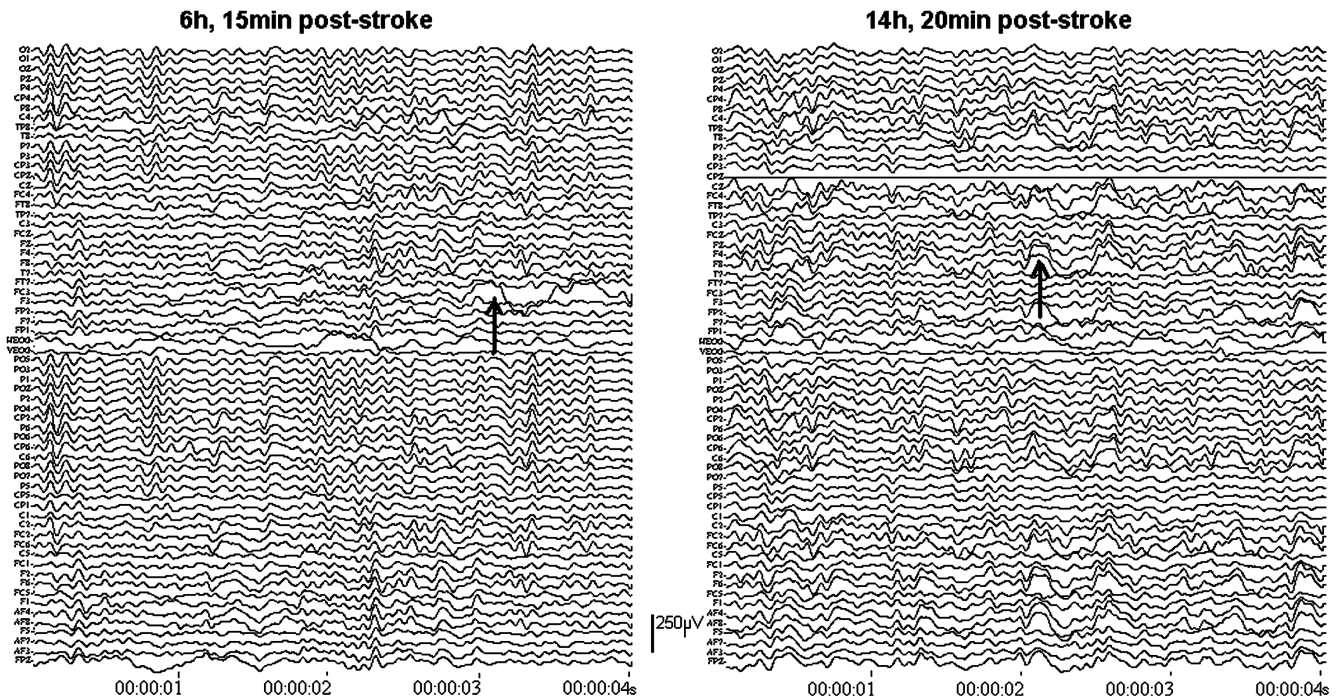


Fig. 3. Representative raw EEG trace exemplars from patient B. These were acquired at two stipulated time-points during the acute post-stroke period, which correspond to the first and third QEEG delta topography maps in Fig. 2. In the trace on left, high-voltage delta oscillations are evident over the ipsilateral (left) hemisphere (e.g., electrode FC3, indicated by the arrow); and some relatively lower-voltage delta oscillations are already evident over the contralateral hemisphere (particularly right frontal electrodes). In the subsequent trace on the right, frequent higher-voltage delta oscillations are evident over the contralateral hemisphere (e.g., electrode F8, indicated by the arrow); whereas these are no longer so evident over the ipsilateral hemisphere. Note the general correspondences between the illustrated delta oscillations in each of these raw EEG traces, and the respective QEEG delta maps illustrated in Fig. 2.

4 h later at 14 h, 20 min post-stroke; and delta power had further increased at these and other CH (temporal) electrodes by this time (see Figs. 2 and 3). The CH delta focus in the initial QEEG data (6 h, 15 min) was relatively more prominent in comparison to the minimal CH abnormality in the DWI data acquired at a similar time. For example, mean QEEG delta power was greater over the CH than IH even at this early time. Moreover the cross-temporal evolution in delta power and scalp topography – incorporating dissipation of the IH delta focus and the concomitant increase in the magnitude and spatial extent of the CH delta maximum – also were substantially more pronounced and relatively more rapid than the corresponding and cross-temporal changes in DWI abnormalities over the corresponding time-frame. In contrast to these pronounced QEEG-delta changes and the DWI changes, the NIHSS score remained unchanged over the same period. The NIHSS score at 27 h post-stroke had increased to 35, and the patient deceased at approximately 44 h, 30 min post-stroke. As was the case for patient A, the emergence of a CH delta power maximum was once again observed to be very salient with regard to prognosis. Again parallel NIHSS observations, particularly the lack of change in NIHSS score over the same period, demonstrated lower efficacy in this regard. DWI observations and acute changes in same, including emergence of a relatively small CH abnormality, also were indicative of worsening cerebral pathophysiology; however it is notable that again in this case, the cross-temporal changes in DWI observations (as well as the degree of CH abnormality relative to IH) were substantially less pronounced relative to those in the corresponding QEEG observations.

The current data converge with and add novel observations to those from a burgeoning literature which attests to the prognostic efficacy of delta-related indices of ischaemic cerebral pathophysiology. In recent years this literature encompasses QEEG investigations in subarachnoid haemorrhage (Claassen et al., 2004), acute (Finnigan et al., 2004, 2006) and sub-acute (Finnigan et al., 2007) ischaemic stroke, as well as MEG observations from sub-acute ischaemic stroke patients (Tecchio et al., 2007; Zappasodi et al., 2007). Consistent with the latter reports, the acute post-stroke shift of scalp delta power maxima from IH to CH indicated substantial worsening of cerebral pathophysiology in the present two cases. Furthermore these QEEG phenomena were more pronounced than parallel DWI changes and they preceded worsening of neurological symptoms and ultimately, the deaths of both patients in the ensuing days. Hence of the current multi-modality observations, CH delta maxima in QEEG data proved most effective for prognostic purposes. To our knowledge this is the first report of emergence of CH delta power maxima within the first 24 h post-stroke, as the MEG observations cited above were acquired between 2 and 10 days post-stroke. In the current data CH delta foci were present by 6 h, 15 min (patient B) and 17 h, 15 min (patient A). In

both cases the increasing CH delta power over time was of sufficient magnitude to force a concomitant increase in delta power averaged across all scalp electrodes, despite a parallel decrease in mean IH delta power. It is salient to note we have not observed CH delta power maxima in EEG from any of the other stroke patients we have previously studied and reported (Finnigan et al., 2004, 2006, 2007); including a patient with an admission NIHSS score of 21 and large DWI abnormality in the LMCA territory, who underwent successful thrombolysis therapy within 6 h and demonstrated substantial recovery (NIHSS score of 7 at 123 days post-stroke). Nor was a CH delta power maximum observed in acute and sub-acute EEG from a MCA stroke patient who survived beyond 30 days post-stroke but whose clinical symptoms significantly worsened over this time (NIHSS score increased from 11 at 7 h, to 22 at 48 h, then was 19 at 30 days post-stroke; Finnigan et al., 2004). In the latter case an acute increase in mean scalp delta power (averaged over all scalp electrodes) was however observed and this was consistent with the subsequent clinical deterioration (Finnigan et al., 2004). A potential explanation for the lack of emergence of a CH delta focus in this patient is briefly discussed below.

Tecchio et al. (2007) review a range of relevant findings from both human and animal studies and hypothesise that increased CH delta activity may be “an expression of early neuronal reorganisation”. Another recent report from the same group suggests that CH delta activity “could be an expression of the dysfunction of intracortical GABAergic neurons” (Zappasodi et al., 2007). While we do not have definitive evidence with which to reject such interpretations, we alternatively posit that emergence of high-voltage CH delta activity primarily reflects herniation (midline shift) associated with substantial oedema in the IH and increased intracranial pressure. The DWI scans illustrated in Figs. 1 and 2 (particularly the second scan from each patient) illustrate to a degree the occurrence of such phenomena. Further, we propose that as the degree of IH infarction progresses, the affected regions move towards electrical silence, hence the somewhat “paradoxical” decrease in mean IH delta power. Collectively the aforementioned pathophysiological phenomena could account for the evolution of CH delta foci such as those observed in the present stroke patients. Additional multi-modality observations from larger patient samples are required to systematically assess these proposals.

Notably, the current data also indicate that a high-density electrode array is not essential and a standard, 19-electrode array appears adequate for the detection of this pathophysiological marker. This is consistent with our previous observations of prognostically-relevant global delta and alpha power measures during sub-acute stroke (Finnigan et al., 2007) and routine usage of a standard electrode array with fewer electrodes renders bedside EEG monitoring more feasible than does a high-density array. We have previously discussed in detail the potential limitations of EEG monitoring such as possible contamination of QEEG

indices by artefacts such as those due to patient movement (e.g., eye movements) and/or by sleep- or drowsiness-related EEG activity (Finnigan et al., 2004, 2007). Although we can again exclude the possibility of such events significantly affecting the current data, such factors remain pertinent. In addition the current data comprise three, relatively brief and intermittent EEG recordings per patient; whereas recordings made continuously over a number of hours should generally be optimal, particularly with regard to closely monitoring cross-temporal changes in EEG and/or in salient QEEG measures such as global delta power (Finnigan et al., 2004), delta/alpha power ratio (Finnigan et al., 2007) or hemisphere-specific delta power.

If potential issues such as those outlined above can be accounted for and if the delta observations presented and cited herein can be replicated in larger patient samples, such QEEG measures may become more routinely utilised in future to inform clinical prognoses and stroke patient management. For example QEEG measures, and cross-temporal changes in same, computed promptly (perhaps automatically) might help guide future clinical decisions about administration or efficacy of an intervention such as local, intra-arterial thrombolysis therapy. Further, in MCA infarction in adults under 60 years, where decompression surgery is being contemplated, such QEEG observations may assist in more timely decisions to operate. In such circumstances QEEG indices should of course be considered in concert with other (e.g. clinical and MRI) concomitant observations.

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 haemorrhage. *Clin Neurophysiol* 2004;115:2699–710.
- 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 Electroenceph* 2003;34:1–4.
- Finnigan S, 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;117:2338–9.
- Finnigan SP, Rose SE, Walsh M, Chalk JB. Quantitative EEG indices of sub-acute ischaemic stroke correlate with clinical outcomes. *Clin Neurophysiol* 2007;118:2525–32.
- Jordan KG. Emergency EEG and continuous EEG monitoring in acute ischemic stroke. *J Clin Neurophysiol* 2004;21:341–52.
- Tecchio F, Pasqualetti P, Zappasodi F, Tombini M, Lupoi D, Vernieri F, et al.. Outcome predication in acute monohemispheric stroke via magnetoencephalography. *J Neurol* 2007;254:296–305.
- van Putten MJAM, Tavy DLJ. Continuous quantitative EEG monitoring in hemispheric stroke patients using the brain symmetry index. *Stroke* 2004;35:2489–92.
- Zappasodi F, Tombini M, Milazzo D, Rossini PM, Tecchio F. Delta dipole density and strength in acute monohemispheric stroke. *Neurosci Lett* 2007;416:310–4.

S.P. Finnigan

Centre for Magnetic Resonance,
The University of Queensland, Qld 4072, Australia
E-mail address: finnigan.simon@gmail.com

Stephen E. Rose

Centre for Magnetic Resonance,
The University of Queensland, Qld 4072, Australia

Jonathan B. Chalk

Centre for Magnetic Resonance,
The University of Queensland, Qld 4072,
Australia
School of Medicine,
The University of Queensland, Australia

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In response to “Correlations of nerve conduction measures in axonal and demyelinating polyneuropathies”

We read with great interest the paper “Correlations of nerve conduction measures in axonal and demyelinating polyneuropathies” by Tankisi et al. (2007). To investigate if the correlation between amplitude reduction and conduction slowing could be helpful in the differentiation between demyelinating and axonal polyneuropathies, the authors performed a retrospective study and evaluated 53 axonal and 45 demyelinating polyneuropathies. Interestingly, they found that decrease in SNAP/CMAP amplitude was more frequent in demyelinating than in axonal polyneuropathies, and also the mean decrease in amplitude was more severe compared to axonal polyneuropathy. The reported results seem to contradict the common belief that a reduction in SNAP/CMAP amplitude is typical of axonal damage while a reduced conduction velocity reveals a prevalent myelin damage. We agree with Tankisi and colleagues (p. 2391, paragraph 5.3) that amplitude evaluation should be considered in demyelinating polyneuropathies. We developed a computerised model to study the relationship between axonal properties and neurophysiological findings in motor nerve patchy demyelination, and to provide a measure of sensitivity of conventional tests in detecting myelin damage (Caliandro et al., 2007). We found that when the myelin damage involves both large and small axons, the conduction velocity is pathological only when severe myelin damage involves a large number of axons, while temporal dispersion of the negative phase and amplitude decay interestingly are more sensitive than conduction velocity in detecting the damage. Tankisi et al. hypothesise (p. 2391, paragraph 5.2) that in their patients with demyelinating polyneuropathy the observed amplitude decay is due to temporal dispersion (Kimura et al., 1988; Olney et al.,