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Evoked potentials recorded during routine EEG predict outcome after perinatal asphyxia

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HIGHLIGHTS

- EEG with simultaneous evoked potential recording is valuable in asphyxic newborns.
- Somatosensory evoked potentials recorded during routine EEG predict outcome with 98% accuracy.
- EEG complemented with SEPs is more accurate than EEG alone in outcome prediction.

ABSTRACT

Objective: To evaluate the added value of somatosensory (SEPs) and visual evoked potentials (VEPs) recorded simultaneously with routine EEG in early outcome prediction of newborns with hypoxic-ischemic encephalopathy under modern intensive care.

Methods: We simultaneously recorded multichannel EEG, median nerve SEPs, and flash VEPs during the first few postnatal days in 50 term newborns with hypoxic-ischemic encephalopathy. EEG background was scored into five grades and the worst two grades were considered to indicate poor cerebral recovery. Evoked potentials were classified as absent or present. Clinical outcome was determined from the medical records at a median age of 21 months. Unfavorable outcome included cerebral palsy, severe mental retardation, severe epilepsy, or death.

Results: The accuracy of outcome prediction was 98% with SEPs compared to 90% with EEG. EEG alone always predicted unfavorable outcome when it was inactive ($n = 9$), and favorable outcome when it was normal or only mildly abnormal ($n = 17$). However, newborns with moderate or severe EEG background abnormality could have either favorable or unfavorable outcome, which was correctly predicted by SEP in all but one newborn (accuracy in this subgroup 96%). Absent VEPs were always associated with an inactive EEG, and an unfavorable outcome. However, presence of VEPs did not guarantee a favorable outcome.

Conclusions: SEPs accurately predict clinical outcomes in newborns with hypoxic-ischemic encephalopathy and improve the EEG-based prediction particularly in those newborns with severely or moderately abnormal EEG findings.

Significance: SEPs should be added to routine EEG recordings for early bedside assessment of newborns with hypoxic-ischemic encephalopathy.

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Abbreviations: aEEG, amplitude-integrated electroencephalography; BE, base excess; CP, cerebral palsy; EEG, electroencephalography; EP, evoked potential; HIE, hypoxic-ischaemic encephalopathy; IBI, interburst interval; MRI, magnetic resonance imaging; NICU, neonatal intensive care unit; SEP, somatosensory evoked potential; VEP, visual evoked potential; TH, therapeutic hypothermia.

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1. Introduction

Hypoxic-ischaemic encephalopathy (HIE) due to perinatal asphyxia occurs in approximately 2.5 per 1000 live full-term births (Graham et al., 2008), and is one of the leading causes of neonatal deaths and severe neurodevelopmental compromise (Lai and Yang, 2011). Recent data show that even when treated with therapeutic hypothermia (TH), 40–50% of newborns with moderate-to-severe HIE will die or develop with severe handicap (Tagin et al., 2012).

Early recovery of the electroencephalography (EEG) background or amplitude-integrated EEG (aEEG) trend has, within the last decade, become a routine bedside method for early prognostication (Hellström-Westas et al., 1995; Toet et al., 1999; Murray et al., 2009). However, TH delays the aEEG recovery beyond the first 36–48 h, limiting its utility in early outcome prediction (Hallberg et al., 2010; Thoresen et al., 2010; Massaro et al., 2012; Csekő et al., 2013; Bonifacio et al., 2015). In terms of early prognostication, the newborns with moderate HIE are the most challenging (Gunn et al., 2008). This very same population may, however, gain the most from therapeutic interventions (Tagin et al., 2012). Hence, it is of high priority to improve the accuracy of outcome prediction at bedside to support individualized treatment decisions.

In addition to EEG, other neurophysiological methods, particularly somatosensory (SEPs) (Majnemer et al., 1990; Taylor et al., 1992; Eken et al., 1995; Scalais et al., 1998; Suppiej et al., 2010; Swarte et al., 2012; Kontio et al., 2013) and visual evoked potentials (VEPs) (Whyte et al., 1986; Muttitt et al., 1991; Taylor et al., 1992; Eken et al., 1995; Scalais et al., 1998; Suppiej et al., 2010) are known to predict clinical outcome after perinatal asphyxia. In the present paper, we set out to study whether recording SEPs and VEPs simultaneously with routine EEG could provide additional value in the early outcome prediction in term newborns with HIE, and whether their predictive yield is affected by TH, an essential part of modern neonatal intensive care.

2. Patients and methods

2.1. Patients (Table 1, Supplementary Table S1)

The study included 50 newborns (born between 36 + 7 and 42 + 2 gestational weeks; 23 females) treated for asphyxia/HIE at the tertiary level neonatal intensive care unit (NICU) of the Helsinki University Hospital during a four-year period (January 2011 – December 2014). Initially, we identified all asphyxiated/HIE newborns within the study period that underwent an EEG. Asphyxia was defined by the following criteria: pH < 7.10, BE ≤ −10 mmol, 5-min Apgar score ≤ 6, or primary mechanical ventilation and some other indication of asphyxia (e.g. abnormal cardiotocography, decreased fetal movements, or meconium in the amniotic fluid). We then excluded newborns with gestational age < 36 weeks and those with diagnosed or suspected genetic abnormalities, inborn errors of metabolism, or major malformations. Only the earliest EEG of those newborns with several recordings was included. All of the final 50 EEG recordings included simultaneous SEPs and VEPs (in accordance with our in-house routine clinical neonatal EEG protocol). All neurophysiological recordings were performed for clinical indications. Of these 50 newborns, 28 received whole-body therapeutic hypothermia (target temperature 33–34 degrees) for 72 h as part of their treatment strategy and 15 of the 28 were still under hypothermia during the EEG and EP recording. Cooling was initiated according to the criteria of the TOBY study (Azzopardi et al., 2008) with the exception that in certain situation cooling was initiated without a preceding aEEG trace (e.g. if aEEG was not available).

The Ethics Committee for Pediatrics, Adolescent medicine, and Psychiatry, Hospital District of Helsinki and Uusimaa, approved the study protocol. Parental consent form was received for the use of the photograph in Fig. 1A.

2.2. Decisions on withdrawal of treatment

Decisions to withdraw intensive care were based on a combination of poor clinical condition including severe HIE, poor EEG, and severe MRI findings. Decisions were made after discussions with parents.

2.3. EEG, SEP, and VEP recording (Fig. 1A and B)

The EEG and EPs were recorded between 15 h and 10 days postnatally, following our in-house developed clinical routines (Nevalainen et al., 2015). We collected the EEG and SEP signals at 2000 Hz using the NicoletOne EEG system (Cardinal Healthcare/Natus, USA; acquisition bandwidth 0.053–500 Hz), Cz reference, and 21 channel EEG caps (sintered Ag/AgCl electrodes; Waveguard, ANT-Neuro, Germany). An additional electrode was placed over the C7 vertebra to record the cervical SEP. We stimulated each median nerve at the wrist at 0.5 ($n = 7$) or 1 Hz ($n = 43$) rates using two disk electrodes and a battery powered portable electrical peripheral nerve stimulator (Micromed Energy Light stimulator; Micromed, Italy) and pulse width of 0.2 ms. If standard stimulation was not possible due to intravenous lines, we stimulated the median nerve at the palm ($n = 7$) or elbow ($n = 1$). One newborn only underwent unilateral stimulation because no suitable stimulation site was accessible on one side. The stimulation current was individually adjusted to just above the motor threshold. VEP stimulations were delivered using a stroboscopic flash at 1 or 2 Hz. We aimed at recording all the evoked potentials during sleep (or quietness in case normal vigilance states could not be identified). However, in each EP condition (right hand SEP, left hand SEP, VEP) three newborns did not fall asleep within the recording time slot or woke up during the recording and were, thus, recorded while awake.

2.4. EEG background grading

Two EEG experts (PN and VM) blinded to the clinical information scored all EEGs independently using previously described criteria (Murray et al., 2009). In case of disagreement, a third EEG expert (LL) scored the given EEG, and the final score was reached by consensus. EEG grade 4 indicated inactive trace (background activity < 10 μ V or severe discontinuity with interburst interval (IBI) > 60 s), grade 3 severe abnormality (discontinuous activity with IBI 10–60 s, severe attenuation of background patterns, no sleep-wake cycle), grade 2 moderate abnormality (discontinuous activity with IBI < 10 s, or clear asymmetry or asynchrony), grade 1 mild abnormality (continuous activity with slightly abnormal activity: e.g., mild asymmetry, or mild voltage depression), and grade 0 normal EEG.

2.5. Analysis of evoked potentials

We averaged the EPs offline in BESA® software (BESA GmbH, Germany) for epochs from −100 to 800 ms relative to stimulus onset without further filtering (Fig. 1C). Author PN visually evaluated all EPs using bipolar montages and electrical field maps (Fig. 1D–E). Cervical SEP was identified in the cervical electrode (C7, referenced to Fz) between 8 and 20 ms. Cortical SEP was observed as a salient response beginning within 100 ms from the stimulation in the contralateral centroparietal area coupled with a topographic pattern of electrical field that indicated a source at the contralateral primary somatosensory cortex i.e. a parietal

Fig. 1. (A) EEG is recorded with a whole-head EEG cap, while (B) the median nerves are consecutively stimulated. (C) Evoked potentials are averaged off-line according to the markers in the EEG data (DIGIN). (D) SEP to right median nerve stimulation in the left central area. The yellow line marks the peak of the first cortical response at 41 ms. (E) VEP in the occipital area. The yellow line marks the peak of the response at 207 ms.

negativity paired with a frontal positivity. Cortical VEPs were observed in the occipital area with onset <300 ms. Cortical SEPs were classified as bilaterally absent, unilaterally absent, or bilaterally

present, whereas VEPs were classified as absent or present. The classification agreement rate with the original clinical EP report was 100%.

2.6. Magnetic resonance imaging (MRI)

Of the 50 newborns, 46 underwent brain MRI (1.5Tesla scanner, Philips Intera Achieva, Philips Medical Systems, Best, The Netherlands) with a clinical imaging protocol including T1-weighted axial, T2-weighted axial and coronal, diffusion weighted axial, and T2 gradient echo axial images. An experienced pediatric neuro-radiologist (author STS) classified the MRIs into six categories according to previously published criteria (Shankaran et al., 2012) (see Supplementary Table S1 for details).

2.7. Outcome

An experienced neonatologist (author MM) determined clinical outcomes by retrospective review of the medical records using the following predefined, outcome categories (see also Iyer et al., 2014): normal, mild abnormality (including mild speech, motor, or cognitive delay), moderate abnormality (including moderate dyskinetic or hemiplegic CP) severe abnormality (including tetra-plegic and/or severe dyskinetic CP, severe mental retardation, and severe epilepsy), or death. Normal and mild abnormality were considered as favorable and moderate/severe abnormality and death as unfavorable outcomes. The outcome scoring was primarily based on an evaluation from the routine follow-up visit to a (neuro)pediatrician between 18 and 30 months age. When this was not available (17 patients) we used the latest available visit between 3 and 16 months age (see Supplementary Table S1 for details).

2.8. Statistics

We calculated the accuracy, sensitivity, specificity, and positive and negative predictive values, including corresponding 95% confidence intervals, for the predefined, dichotomic neurophysiological results: Poor EEG was taken as grade 3–4, poor SEP as absent response on at least one hemisphere, and poor VEP as an absent response.

3. Results

EEG grade and presence/absence of EPs were all predictive of outcome (Fig. 2). The prediction accuracy was highest with SEPs (98%), followed by EEG (90%), and lowest with VEPs (84%). Specificity, sensitivity, and positive and negative predictive values for each method and their combinations are shown in Table 2. In the clinically most challenging group of 24 newborns with moderate-to-severe EEG background abnormality (grade 2 and 3), the accuracy of outcome prediction with EEG was 79%, whereas accuracy of prediction with SEP was 96%.

EEG and SEP results with respect to postnatal age during the recording are shown in Fig. 3. For those recordings performed within the first 48 h, the prediction accuracy of SEP was 100% and that of EEG 93%. In the subgroup of newborns that received therapeutic hypothermia the prediction accuracy of SEPs was 100%, and that of EEG 96%.

Individual EEG and EP results, together with the corresponding clinical details and MRI scores, are presented in Supplementary Table S1. Of the 50 newborns, EEG showed grade 4 background abnormality in nine newborns, of whom SEPs were bilaterally absent in eight and unilaterally absent in one. All nine had a poor outcome (six died in the neonatal period, three developed severe disability and one of them died at 5-months of age). EEG grade 3 was observed in eight newborns. SEPs were bilaterally absent in four and unilaterally absent in one of them, and all five had an unfavorable outcome (one died and four developed with moderate

Fig. 2. Flow diagrams: association between EEG, SEP, and outcome. Black squares mark poor test result/unfavorable outcome, and white squares mark good test result/favorable outcome. Numbers within squares mark the number of newborns. SEP– = SEP bilaterally absent, SEP+/- = SEP unilaterally absent, SEP+ = SEP bilaterally present, † = number of deaths, * = hemiplegic cerebral palsy.

Table 1
Baseline characteristics of the study population.

Baseline characteristic	N = 50
Females	23 (46%)
Received TH	28 (56%)
Under TH during EEG-EP	15 (30%)
GA	40 [1,5] weeks
Postnatal age at EEG-EP	45[66] h
Birth weight	3330 [630] g
BE	−13,5 [5,9]
pH	7,0 [0,2]
Apgar 1 min	1{1}
Apgar 5 min	3{4}
Apgar 10 min	5{3}

Data shown as n (%), mean [SD], or median [IQR]. TH = therapeutic hypothermia, GA = gestational age, EP = evoked potential, BE = base excess.

or severe disability). On the contrary, three newborns with EEG grade 3 but present SEPs had a favorable outcome. EEG grade 2 was observed in 16 newborns, one of which had unilaterally absent SEP and an unfavorable outcome (moderate disability, hemiplegia). Of the remaining 15 newborns with SEPs present bilaterally, fourteen had a favorable outcome, but one (not receiving hypothermia) developed severe disability. This newborn had the largest asymmetry in SEP onset latency (8 ms vs other newborns' median 1 ms, range 0–6 ms), which was, however, not part of the predefined SEP criteria. EEG was normal or only mildly abnormal (grade 0 or 1) in the remaining 17 newborns. All of them had bilateral SEPs, and a favorable outcome. VEPs were absent in eight of the nine newborns with grade 4 EEG, and present in all the other 42 newborns.

4. Discussion

Our data show that assessment of evoked potentials simultaneously with a routine EEG provides a reliable bedside tool for early outcome prediction in term newborns with HIE. In line with previous literature (Pressler et al., 2001; Murray et al., 2009; Hamelin et al., 2011), normal or mildly abnormal EEG background was invariably associated with a favorable outcome, while an inactive EEG predicted an unfavorable outcome. Newborns with moderate-to-severe EEG background abnormality (EEG grade 2–3) could have either outcome, which was, however, reliably predicted by the simultaneous SEP. Absent VEPs were only observed in the newborns whose unfavorable outcome was already predicted correctly by the inactive EEG.

4.1. Challenges in early outcome prediction after perinatal asphyxia

Early outcome prediction in asphyxiated newborns is essential for guiding individual treatment decisions, but it is complicated by the combination of rapidly changing neurological state during

Table 2

Predictive values of poor EEG, SEPs, and VEPs and their combinations for an unfavorable outcome.

Method(s)	Specificity	Sensitivity	PPV	NPV
EEG	91 (76–98)	88 (62–98)	82 (57–96)	94 (80–99)
SEP	100 (90–100)	94 (70–100)	100 (78–100)	97 (85–100)
VEP	100 (90–100)	50 (25–75)	100 (63–100)	81 (66–91)
EEG and SEP	100 (90–100)	88 (62–98)	100 (77–100)	94 (81–99)
EEG and VEP	100 (90–100)	50 (25–75)	100 (63–100)	81 (66–91)
EEG and SEP and VEP	100 (90–100)	50 (25–75)	100 (63–100)	81 (66–91)
EEG or SEP	91 (76–98)	94 (70–100)	83 (59–96)	97 (84–100)
EEG or VEP	91 (76–98)	88 (62–98)	82 (57–96)	94 (80–99)
EEG or SEP or VEP	91 (76–98)	94 (70–100)	83 (59–96)	97 (84–100)

NPV = negative predictive value; PPV = positive predictive value. Specificity, sensitivity, PPV, and NPV represent percentage (95% confidence interval). Poor EEG = grade 3 or 4; poor SEPs = SEP absent from at least one hemisphere; poor VEPs = VEPs absent.

Fig. 3. Postnatal age at the time of EEG-EP recording. The circles represent individual newborns: black circles indicate newborns with unfavorable and white circles newborns with favorable outcome. The dashed line marks a change in the time scale.

recovery from HIE, possible secondary injury, and the hypothermia treatment. Several parameters measured at birth (e.g. Apgar score, and severity of acidaemia) are associated with outcomes but, individually, they tend to have poor predictive accuracy (Merchant and Azzopardi, 2015). The clinically determined grade of HIE (Sarnat and Sarnat, 1976) by itself predicts later outcome, but newborns with moderate HIE present a clinical challenge as their outcomes vary considerably (Gunn et al., 2008). Neonatal MRI is highly predictive of outcome, both in normothermic (Rutherford et al., 1998) and TH-treated HIE newborns (Rutherford et al., 2010; Cheong et al., 2012), but it is not available at bedside, and the severity of injury may in some cases be underestimated during the first two days after birth (Barkovich et al., 2006).

4.2. EEG in outcome prediction

EEG is widely used for early outcome prediction in asphyxiated term newborns. Our present results support the general consensus that a normal or mildly abnormal EEG background during the first postnatal days is predictive of a favorable outcome (Pressler et al., 2001; Murray et al., 2009; Hamelin et al., 2011). On the contrary, a severely abnormal EEG after hypoxic-ischemic insult only predicts a poor outcome if it fails to recover within the first day (Pressler et al., 2001; Murray et al., 2009). Observing this recovery, has been the basis for aEEG-based outcome prediction until the introduction of TH, which turned out to significantly delay the aEEG recovery during the first days of life (Hallberg et al., 2010; Thoresen et al., 2010; Massaro et al., 2012; Csekő et al., 2013; Bonifacio

et al., 2015). Our work, together with prior studies (Pressler et al., 2001; Murray et al., 2009; Hamelin et al., 2011) that have evaluated the grade of EEG background abnormality in more detail, show that an inactive or extremely discontinuous (IBI > 60 s) EEG on the second postnatal day or later invariably predicts unfavorable outcome, whereas a clearly, but not as severely, discontinuous pattern (IBI 10–60 s) may lead to either unfavorable or favorable outcome (Murray et al., 2009). This suggests a need for improved methods to extract signatures of brain viability from among the burst suppression backgrounds (Iyer et al., 2014). Our present work demonstrates that SEPs may aid in outcome prediction in this particular group of infants.

4.3. Evoked potentials in outcome prediction

Evoked potentials assess the functional integrity of the given sensory system including key pathways in the deep brain structures (e.g. thalami and brainstem), which are known to be vulnerable to perinatal asphyxia (Gunn and Bennet, 2009). Studies in non-human primates suggest that compared to isoelectric EEG, cortical SEPs would be lost at slightly lower cerebral blood flow values, and thus at a level of ischemia nearer to the true critical level for neuronal damage (Dong et al., 1986). Prior studies in normothermic HIE newborns have repeatedly shown that bilaterally absent SEPs (Eken et al., 1995; Scalais et al., 1998; Suppiej et al., 2010; Swarte et al., 2012) and VEPs (Whyte et al., 1986; Muttitt et al., 1991; Taylor et al., 1992; Eken et al., 1995; Scalais et al., 1998; Suppiej et al., 2010) are highly predictive of an unfavorable

outcome, and bilaterally present SEPs strongly predictive of a favorable outcome (Taylor et al., 1992; Eken et al., 1995; Scalais et al., 1998; Suppiej et al., 2010; Swarte et al., 2012), whereas normal VEPs have lower prognostic value (Taylor et al., 1992; Suppiej et al., 2010) (but see also Whyte et al., 1986; Muttitt et al., 1991; Scalais et al., 1998). Reports on the predictive yield of unilaterally absent SEPs or delays in SEP latencies have been more variable (Eken et al., 1995; Suppiej et al., 2010; Swarte et al., 2012). Previous studies have, however, used a limited number of recording electrodes, whereas we used multichannel SEP assessment including offline averaging and montaging for an improved SEP identification. We believe that these methodological advances improved the accuracy enough to show that also all newborns with unilaterally absent SEPs had an unfavorable outcome. Importantly, since our method – simultaneous EEG and SEP recording – allows interpreting SEPs with the knowledge of spontaneous cortical (EEG) activity, we were able to show that SEPs could distinguish the newborns with favorable and unfavorable outcome in the challenging group of 8 newborns with discontinuous EEG background (grade 3). Bilaterally present SEPs predicted favorable outcome with the exception of only one newborn. Our posthoc analysis suggested that this newborn had an exceptionally large asymmetry (8 ms) in cortical SEP onset latency, which was not part of our predefined SEP criteria. Future studies with other datasets are needed to define whether onset latency asymmetry could be a useful criterion to perfect the SEP-based prognostication.

A key advantage of SEPs compared to EEG is its resistance to therapeutic levels of hypothermia, which is clearly documented both in experimental animals (Madhok et al., 2012) and in adults treated with TH after cardiac arrest (Sandroni et al., 2014). Similarly, in the present study, TH did not lower the predictive yield of SEPs as the only newborn with bilaterally present SEP but poor outcome did not undergo TH. On the contrary, a recent study in asphyxiated newborns reported only 36% PPV for bilaterally absent SEPs in predicting moderate-to-severe disability (Garfinkle et al., 2015). We suggest that several methodological differences would readily explain the markedly higher accuracies in our work: The previous study (i) recorded patients during the second week of life only; (ii) used higher stimulation frequency that is known to deteriorate SEPs in young infants (Araki et al., 1999); (iii) used only two recording electrodes as opposed to our 21 electrodes, which according to our experience will lead to ignoring at least some of the responses. Indeed, this comparison illustrates the need to reconsider neonatal SEP protocols so that they take into account the highly focal nature of neonatal scalp potentials (Odabae et al., 2013) (i.e. more electrodes needed), and the sensitivity to stimulation frequency (Araki et al., 1999).

4.4. Limitations of the study

Our work was retrospective and hence we could not assess the genuine clinical impact of our EEG-EP results on actual treatment decisions. We acknowledge, that together with other clinical information and neuroimaging, EEG and to a lesser extent EPs were used in clinical decision-making concerning redirection of care, which introduces the possibility for a self-fulfilling prophecy. However, all newborns that died after redirection of care ($n = 5$) had clinically severe HIE (grade 3) and severe structural brain injury on MRI (grade 2B or 3, Supplementary Table S1), which are both strong independent predictors of a poor prognosis. Thus, it is likely that the outcome had been poor, even if the intensive care had been continued. Another limitation is the timing of the EEG-EP recording, which was not standardized but instead determined by the clinical question, preventing us from determining the best timing for the SEP assessment. An earlier timing of the EEG-EP recording should, however, be explored in the future to confirm a

previous SEP study showing that false positive SEPs (i.e. absent SEPs associated with favorable outcome) may not be a true risk in asphyxiated newborns (Eken et al., 1995). Finally, as the follow-ups were organized according to clinical need, also their timing varied. We do, however, suggest that the follow-up information is sufficient for determining the robust outcome categories of the present study i.e. favorable vs. unfavorable.

5. Conclusions

This is the first study in asphyxiated newborns combining the information from simultaneously recorded EEG and EPs, which allows evaluation of EPs in the context of the brain state, particularly the spontaneous EEG background and/or sleep stage. It is conceivable that, for instance, the clinical inference of a unilaterally absent SEP together with only moderately abnormal EEG background (i.e. focal or limited brain injury) is fully different from observing unilaterally absent SEP together with an inactive EEG and absent VEP (widespread, severe injury). Hence, our results as a whole are advocating multimodal recording rather than replacement of EEG with evoked potentials.

Recording evoked potentials as a part of routine EEG is feasible, cheap, saves time, and causes minimal extra discomfort to the sick newborn. Combination of EEG and SEPs accurately predicts outcome in HIE newborns during the first days of life regardless of therapeutic hypothermia, gives a more comprehensive measure of brain function than the methods do alone (or when performed separately), and holds, thus, promise for clinical use in the future.

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Conflict of interest: The authors have no conflicts of interest relevant to this article to disclose.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.clinph.2017.04.025>.

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