Near-Infrared Spectroscopy in Stroke: From Research to Clinical Practice

To the Editor:

We read with interest the editorial comment by Villringer and colleagues on the use of near-infrared spectroscopy (NIRS) as a routine diagnostic tool in stroke. We agree that NIRS has great potential to become a valuable bedside tool; however, several limitations need to be overcome.

Crucial to the successful use of NIRS is an appreciation of its ability to measure real-time changes in cerebral hemoglobin oxygen saturation. These equate to changes in cerebral blood volume only and not necessarily cerebral blood flow and may consequently lead to misinterpretation of clinical data. The relative contribution of different vascular compartments to the NIRS signal also needs to be established as it is not known whether venous changes in oxygenated hemoglobin makes a greater contribution than arterial changes. Extracranial tissues: melanin-containing skin, lipid-prevalent soft tissue, bone, and cerebrospinal fluid may also absorb a significant proportion of infrared light. This makes absolute intrapatient comparisons difficult. Even in individual patient analyses extracranial tissues may elicit varying degrees of absorption with changes in their extracranial blood supply. Attempts to quantify this contribution have proved difficult whether studying patients at carotid endarterectomy or using Monte Carlo simulation. Smielewski and colleagues however suggest that cerebral oxygenation, as recorded by NIRS and cutaneous laser-Doppler flowmetry, is largely unaffected by extracranial tissue perfusion. More work is needed to understand the behavior of near-infrared light in different biological tissues if NIRS is to be used as a reliable clinical monitor.

NIRS use as a research tool in measuring cortical activation may help in the understanding of dynamic remodeling which may occur within brain architecture during neuroplasticity post-stroke. The work of Kato and colleagues using NIRS in conjunction with functional MRI has lent support to the role of activation with functional MRI has lent support to the role of activation in real-world environments outside the neuroimaging "tunnel."

In summary, there is great potential both acutely and in the rehabilitation setting for NIRS. Qualifying some of the uncertainties around its use will be a necessary precursor to its acceptance, reliability, and use in routine stroke care.

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Response:

We fully agree that a critical evaluation of optical topography is required when applied in a clinical context as you point out in the comment regarding our editorial comment. Certainly the methodology can as yet not be used in a way similar to neurosonological approaches (transcranial and extracranial Doppler sonography) but it may well gain a similar status with a focus on neuromonitoring in intensive care settings. We are convinced that beyond it being generally wise to follow a skeptical approach when introducing a novel methodology into clinical research, a number of basic tasks are worth the joint effort to establish noninvasive cerebral optical spectroscopy beyond a purely scientific context (for review see). The following applications seem attainable in near future:

Perfusion Imaging

There is a number of first attempts to use dye-bolus technique to assess a measure of cerebral perfusion. Though exact mean transit time (MTT) assessment may be the gold standard, it should not be forgotten that a quasi-continuous assessment on a stroke unit may be an exquisite option to monitor the patient. Interhemispheric perfusion differences, even if only semiquantitative, may still help us understand pathophysiological relevant and potentially treatable changes in perfusion caused by recanalization after embolic occlusion of the larger vessels in acute stroke. This has been done using TCD but will greatly profit.
even from a qualitative assessment of cortical perfusion. There is no need to replace the standard methods; on the contrary, insonation of the large vessels and spectroscopic investigation of cortical perfusion will be complementary. Ideally it will be combined with the high spatial resolution of perfusion weighted MR imaging performed at larger intervals.

**Functional Stimulation**

There is no reason why the large number of functional stimulation studies performed with near infrared spectroscopy should not be directly transferred to a bed-side assessment in patients suffering from neurovascular or neurodegenerative diseases. The major problem here rather is the reluctance of clinical practice to focus on functional rather than structural brain imaging. The traditional exception is electroencephalography (EEG) and the assessment of visually, somatosensory, and acoustically evoked potentials (VEP/SSEP/AEP), which have been used for decades. The slow introduction into clinical practice is by no means specific to optical methods; Functional magnetic resonance imaging (fMRI) and positron emission tomography share a similar problem. Because spatial resolution of optical topography will most probably not reach that of fMRI techniques, primary cortical areas (motor and visual) may serve as indicators of a normal or disturbed neurovascular coupling. Much like evoked potentials, this will help link evidence of structural lesions (as seen in routine imaging approaches) to the clinical examination (which by no means is objective but still the gold standard when therapeutic success is evaluated).

**Neurovascular Coupling**

It has been suggested that a number of neurological diseases interfere with the physiologically tight coupling between neuronal and vascular response. This can be assessed with low-cost, undemanding set-up and at the bed-side when EEG-techniques and optical topography are combined. Again, the major obstacle is the fact that clinical studies require a longer and potentially very tedious approach, and as yet few representative studies have been published. This again is a limitation, which necessitates adequate funding rather than shedding doubt of the versatility of optical methods as such.

Our impression is that the state of the art methodological approaches of noninvasive optical imaging techniques presently do allow for studies relevant to clinical practice. The major shortcoming is the reluctance to challenge the method in larger studies, with representative numbers of patients included. At the same time, the research into physiological mechanisms of functional activation has been established. In cooperation with physicists and a practice-oriented engineering effort, cortical functional activation is bound to reach much higher topographical and depth resolution in the very near future.

**The Need to Recognize the Difference Between a Quality Register and a Randomized Controlled Trial**

To the Editor:

In the pursuit of new data on thrombolysis with recombinant tissue plasminogen activator (rtPA) in patients with acute ischemic stroke, clarity is needed on what information can be obtained from different methods; ie, observational methods, like a quality register, and experimental methods, like a randomized controlled trial (RCT).

Apart from treatment in a stroke unit that benefits all stroke patients, thrombolytic therapy for acute ischemic stroke is at present the only medical treatment available, and is by far the most promising. To date 2955 patients have been randomized into trials with intravenous rtPA. Systematic reviews of the trials showed that, despite the hazards of intracranial hemorrhage and early death, there is scope for benefit from thrombolysis up to 6 hours. Based on the first positive thrombolysis trials in 1995, treatment with rtPA has been licensed in USA and Canada for use within 3 hours of stroke onset for a selected group of patients. Since 2002 there is a provisional license in the European Union for treatment within 3 hours in even more selected patients, 80 years of age or younger. The licensing will be renewed after 3 years if (1) a further randomized trial (ECASS 3; in patients at 3 to 4 hours after onset) is performed by the manufacturer; and (2) safety (as recorded in the quality register SITS-MOST) is satisfactory among patients treated within the license. These conditions highlight the need to appreciate that an RCT must have adequate statistical power to give reliable answers and whether a treatment register can give valid answers to safety issues.

The difference between a quality register and an RCT seems important to elucidate. Quality registers are based on registration of data on patients treated in ordinary clinical practice according to the type of ischemic stroke, whereas RCT is the gold standard for demonstrating the general therapeutic effect of therapies. In the absence of positive Phase III trials, the licensing of rtPA is based on clinical trials that included patients of a specific age, and those not included in the trials are not covered by the license.

**Main Uncertainties for Intravenous Thrombolysis With rtPA up to 6 Hours in Patients With Acute Ischemic Stroke**

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<th>Uncertainty</th>
<th>Description</th>
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<td>1. Estimations of effect in the individual trials</td>
<td>Uneven effect due to patient heterogeneity</td>
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<td>2. Effect of rtPA on death from all causes</td>
<td>Risk of intracranial hemorrhage</td>
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<td>3. Effect on functional outcome, heterogeneity, and imprecise estimates</td>
<td>Need for long-term follow-up</td>
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<td>4. Effect in older people</td>
<td>Reduced efficacy in elderly patients</td>
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<td>5. Safety in older people</td>
<td>Increased risk of complications</td>
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<td>7. CT features reliably predicting response to thrombolysis</td>
<td>Variability in response to treatment</td>
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<td>10. Implication of the type of ischemic stroke</td>
<td>Different effects on various stroke types</td>
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