Non-invasive optical imaging of stroke

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The acute onset of a neurological deficit is the key clinical feature of stroke. In most cases, however, pathophysiological changes in the cerebral vasculature precede the event, often by many years. Persisting neurological deficits may also require long-term rehabilitation. Hence, stroke may be considered a chronic disease, and diagnostic and therapeutic efforts must include identification of specific risk factors, and the monitoring of and interventions in the acute and subacute stages, and should aim at a pathophysiologically based approach to optimize the rehabilitative effort. Non-invasive optical techniques have been experimentally used in all three stages of the disease and may complement the established diagnostic and monitoring tools. Here, we provide an overview of studies using the methodology in the context of stroke, and we sketch perspectives of how they may be integrated into the assessment of the highly dynamic pathophysiological processes during the acute and subacute stages of the disease and also during rehabilitation and (secondary) prevention of stroke.

Keywords: near-infrared spectroscopy; non-invasive optical imaging; stroke; cerebral perfusion; autoregulation

1. Introduction

From a clinician’s perspective, stroke1 is defined as the sudden onset of a neurological deficit. From the patients’ perspective, the lack or the unspecific nature of warning signs and the commonly painless onset of symptoms still prevent prompt admission to an emergency room for many patients. However, *Author for correspondence (obrić@cbs.mpg.de).

1The terminology is somewhat variable in different countries. In this paper, ‘stroke’ is used to denote ischaemic stroke unless noted otherwise. In some countries, including the authors’, ‘stroke’ as a clinical differential diagnosis includes both ischaemia and haemorrhage, since clinical presentation and risk factors are similar and differentiation requires neuroimaging with computed tomography or magnetic resonance imaging.

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the last decade has seen major advances in the management of acute stroke. This is largely due to two therapeutic inventions that have been established to improve outcome: causal therapy of the focal ischaemia by thrombolysis [1] and (sub)acute monitoring of patients in specialized stroke units [2,3]. While the focus on the (sub)acute phase of stroke is beneficial beyond doubt, the burden caused by stroke by far outlasts this acute stage. The patient’s personal suffering and also the resulting suffering in his or her social environment [4] plus the socioeconomic costs [5,6] of what is usually a lifelong disability cannot be overestimated [7]. Additionally, with regard to the time prior to ischaemic stroke, it is relevant to consider that, in most cases, vascular pathology evolves over years and will often progress after the first event. In sum, it seems adequate to conceive of stroke as a chronic disease. Conceptually, three partially overlapping stages can be differentiated (figure 1): (i) chronic evolution of vascular pathology pertaining to primary and secondary prevention, (ii) (sub)acute stroke requiring hospitalization and (iii) rehabilitative efforts including restoration of abilities or compensation for the patient’s disabilities. The latter may last years in in-patient, out-patient and home-based settings.

(a) The acute stage of stroke

With regard to the diagnostic procedures applied in these stages, the most dramatic advance has been reached in the acute diagnostic stage by the introduction of diffusion- and perfusion-weighted magnetic resonance imaging (dwMRI and pwMRI). Starting minutes after the ischaemic event, dwMRI
provides an operational delineation of the core of the infarcted tissue [8,9]. Additionally, pwMRI, relying on the application of a bolus of contrast agent (gadolinium diethylenetriamine pentaacetic acid, Gd-DTPA), delineates the potentially larger area suffering a perfusion deficit. In the latter, low perfusion constitutes the loss of neuronal function but reperfusion may prevent irreversible infarction of the tissue at risk [10]. Because both areas determine the initial deficit, clinical presentation does not allow for a differentiation. The operational definition of ‘tissue at risk’—derived from the pathophysiological concept of the penumbra [11]—is of supreme relevance to decisions on acute intervention, notably when the option of an extended time window for thrombolysis is discussed [12,13]. Hence, in the acute phase of the disease, MRI techniques (including MR angiography) can be considered as the gold standard for diagnosis. Feasibility and superiority to conventional assessment based on computed tomography (CT), which only allows reliable exclusion of a haemorrhage in the first 6 hours, has also been established in clinically realistic hospital settings [14].

Exclusion of cerebral haemorrhage, by CT or MRI, is constitutive for any acute intervention in ischaemic stroke. Although routinely performed in most ‘Western’ countries, CT/MRI may not be available to all acute stroke patients worldwide. Hence, less cost-intensive techniques—including optical imaging (OI)—have been probed as a screening tool for intracerebral haemorrhage [15]. However, the most decisive differential diagnosis, hypertensive intracerebral haemorrhage, is typically located in the deeper parts of the brain [16], and is thus not directly accessible to non-invasive OI. While subdural, epidural, traumatic and atypical lobar haemorrhage affect parts of the brain that can be interrogated by OI, their presentation, risk factors or relative rarity may not justify advocating OI as a relevant tool for the differential diagnosis between ischaemic and haemorrhagic strokes [17–19]. The potential of the methodology with regard to the detection of a haemorrhage may thus be limited to infants and (premature) neonates, in whom tomographic approaches have yielded promising results [20–22].

(b) The subacute stage of stroke

In the subacute stage, admission to specialized stroke units has successfully been shown to result in fewer deaths and better outcome also in settings outside of clinical studies [23,24]. Interestingly, however, this effect is based on the careful monitoring of mostly internal medicine parameters, including blood pressure, oxygenation, respiration, blood glucose [25,26], body temperature [27] and continuous electrocardiogram (ECG). Additionally, therapeutic interventions like dysphagia control [28] and prompt supply of rehabilitative efforts [29,30] are included in most guidelines [31–37]. Regularly performed clinical neurological assessment is the only specifically neurological monitoring component recommended. It is a clinically detected deterioration that warrants repeated neuroimaging by MRI or CT in most cases. Clearly, in this phase of stroke, a method to continuously monitor the pathophysiological changes in the diseased tissue seems highly desirable. To allow a routine introduction of such ‘brain monitoring’ on stroke units, it is mandatory that the methodology is widely available, easily applicable at the bedside and affordable to centres outside large research-oriented institutions. OI is generally suited to meet these requirements, and a number of studies have investigated its potential (as discussed in §4).
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(c) Stroke prevention

Concerning primary and secondary prevention of ischaemic and haemorrhagic strokes, risk reduction is the target. This largely depends on efficient treatment of the well-established modifiable risk factors, while considering genetic and age-related non-modifiable risks [38]. Since primary prevention includes the general population and secondary prevention needs to be provided to the increasing number of patients after their first stroke, requirements on novel methodologies in this field are even more stringent. It is obvious that a methodology adding to a better definition of proven or potential risk factors must be applicable in a broad out-patient setting, in a general physician’s office, and cannot be cost intensive or make high demands on personnel. Likewise, thorough application of the clearly established secondary prevention measures may be more effective [39] than extending the long-term monitoring of parameters made available by novel techniques. This does not apply to stroke prevention in short-term high-risk situations such as cardiac bypass surgery and carotid artery desobliteration. The potential of OI in this context has been demonstrated in a number of larger-scale studies and has been acknowledged in a number of reviews (see §5).

(d) Guiding rehabilitation after stroke

With regard to the (usually long-term) disabilities resulting from stroke, rehabilitation of sensorimotor and cognitive functions including language has emerged from being a purely therapeutic interest to a key area of cognitive brain research. The demonstration of the fact that functional and structural plasticity can be elicited even by short-term training in adults [40,41] has spurred the search for the underlying neuronal mechanisms [42] and potential interventions to facilitate them [43–45]. OI does not allow assessment of structural changes but has been successfully used to address the question of whether functional activation patterns may be used to track functional reorganization after stroke. Here, the major advantage over the much finer-grained and differential image provided by MRI techniques is the option to assess whole-body movements (e.g. gait) and the perspective to allow ‘on-line’ monitoring of rehabilitative efforts or even biofeedback approaches [46,47]. Some of these exciting perspectives are reviewed in §7 of this paper.

2. The potential of non-invasive optical imaging

We here review a rapidly increasing number of studies exploring the potential of OI based on the principles of near-infrared spectroscopy (NIRS). We use the term OI throughout the text, although, in most instances, only a few probe locations are used. In doing so, we wish to highlight the fact that, in principle, all approaches reviewed can be extended to an imaging approach ideally covering the whole surface of the head. Section 6 reviews studies using functional NIRS, based on the brain’s vascular response to specific stimulation designs. In this latter field, NIRS now regularly provides ‘images’ of at least parts of the surface of the brain in healthy adults, children and also in-patients. We follow the sketched conceptualization of stroke as a chronic disease and divide our review according
to the three stages of the disease (see figure 1). First, we critically discuss studies that focus on supplemental monitoring of stroke patients in the emergency room and in the stroke unit. Next, we give an overview of studies that have addressed the versatility of OI for stroke prevention. This is largely a body of literature on monitoring during cardiac and vascular surgery. However, there are a number of exciting new studies that deal with the issue of autoregulation and its impairment in vascular disease, which we include in this section. In the last section, we ask what potential the method holds in stroke rehabilitation. Studies reviewed in this section mostly address brain plasticity, often with a more basic scientific motivation. However, in this field, a number of very promising approaches have been reported, which may also open a clinical perspective. This perspective is a scientifically empowered approach to novel strategies to lessen the burden of disability with effective rehabilitation.

Before we start our review of the studies, we will provide a brief overview of the parameters accessible to OI measurements and discuss their methodological potential and limitations.

### 3. Parameters and methodological approaches

**(a) Changes in haemoglobin concentrations**

Changes in the concentrations of oxygenated haemoglobin (HbO), deoxygenated haemoglobin (HbR) and their sum, total haemoglobin (HbT), where $HbT = HbO + HbR$, have been determined since the method was first reported \[48\]. Today, oxygenation changes can be determined with multi-channel systems returning topographic images with a spatial resolution in the centimetre range \[49\]. The success of these parameters results from the simplicity by which they are determined. Apart from the appropriate choice of optical wavelength combinations \[50\], no further complex analysis such as modelling of photon migration is needed. Although widely reported when OI is used as a functional imaging tool (see §6), changes in the concentrations of haemoglobins by themselves may not be of much use in the monitoring of (sub)acute stroke. Since absolute quantification of HbO and HbR is not yet reliable enough to allow the definition of thresholds for ischaemia, applications in acute stroke often use standardized procedures (e.g. head tilt) or spontaneous fluctuations of HbO and HbR to assess autoregulation in the diseased tissue (see §4).

**(b) Blood and tissue oxygenation**

There have been several attempts to define a parameter that avoids the issue of absolute quantification of HbR and HbO but still supplies a value that can be used as a threshold to monitor the brain during operations and potentially also in (sub)acute stroke care. Such values usually target cerebral blood or tissue oxygenation ($rSO_2$: regional oxygen saturation; TOI: tissue oxygenation index). The idea behind using derivations of the basic parameters (e.g. $rSO_2^{cerebral} = [HbO]/[HbT]$) is that some of the unknowns like optical background properties characterized by absorption and effective scattering coefficients ($\mu_a/\mu'_s$) and thickness of the extracerebral layers should cancel out. A few groups have hence advocated ‘cerebral oximetry’, especially in the monitoring of intra-operative
stroke risk [51,52]. However, the derived parameters still rely on a number of strong assumptions, rendering their validity questionable for a more widespread use [53–56]. The terms blood and tissue oxygenation are used interchangeably in the literature. This is due to the fact that blood oxygenation usually implies oxygenation in the capillary bed. Oxygenation in the capillaries correlates with oxygenation in the tissue, and the gradient between the capillary and the neuronal tissue is far below the resolution of any non-invasive imaging technique (including MRI). With regard to NIRS, the spatial resolution does not even allow the differentiation between larger vessels and capillaries. However, changes in the blood oxygenation of larger vessels have been shown to contribute minimally to the oxygenation changes as assessed by NIRS, since the high concentration of haemoglobin in these vessels leads to complete absorption irrespective of the oxygenation of the haemoglobin [57,58]. Alternatively, the cytochromes in the respiratory chain can provide a marker of tissue oxygenation. This has been targeted by the attempt to measure changes in the redox state of cytochrome c oxidase using NIRS.

(c) Cytochrome c oxidase

Besides the haemoglobins, the redox state of cytochrome c oxidase (Cyt-ox), the terminal enzyme of the respiratory chain, also contributes to changes in the NIR spectrum of cortical tissue. However, Cyt-ox concentration in the brain is low compared with that of the haemoglobins and its contribution to the difference spectrum has been controversial. The calculation of the redox change of the enzyme may be erroneous owing to the simplified assumptions inherent in the modified Beer–Lambert approach [59]. Today, very few authors report changes in Cyt-ox, and its application in monitoring stroke may be limited [60–63].

(d) Cerebral perfusion and blood flow

Since stroke is caused by a reduction of cerebral blood flow (CBF), the ability of OI to monitor cerebral perfusion has been a focus of research on the potential of a ‘blood flow index’ [64,65]. To obtain such an index, a light-absorbing dye (ICG, indocyanine green) is intravenously applied as a bolus. The passage of the bolus through the tissue interrogated by OI can be determined in analogy to concentration changes in the haemoglobins when the wavelength used matches the absorption spectrum of ICG. Another challenge is that the contrast agent also circulates in the extracerebral tissue (scalp, skull), requiring techniques that allow a differentiation of extra- versus intracerebral signal contribution [66,67]. To extend this approach into a potentially widely applicable monitoring tool, the major technological challenge is to devise an easy-to-use device to allow large clinical studies. These could ultimately depend on its versatility in prediction and improvement of outcome.

Also targeting blood flow in the cerebral tissue, ‘diffuse correlation spectroscopy’ (DCS) or ‘diffusing wave spectroscopy’ is an optical technique that has been shown to characterize blood flow in deep tissues. DCS has the same light penetration as NIRS but provides a much more direct measure of CBF [68]. The method detects the temporal intensity fluctuations of light scattered from moving red blood cells. The detected signals are dependent on the amount and the speed of the moving blood cells and thus provide measurements of relative
CBF. Recently, first experiments assessing cerebral autoregulation in acute stroke in patients have been reported [69]. In particular, in combination with absorption spectroscopy, rendering changes in HbO and HbR, experimental and clinical studies may further the application of this exciting technique.

(e) Depth resolution

For all the parameters outlined in this section, depth resolution is a major issue, since it yields specificity as to whether the brain as opposed to the scalp and skull is really monitored. This may be true for any application of non-invasive OI based on NIRS targeting the adult brain. However, there is a major difference whether OI is used as a functional neuroimaging tool or when it is applied in pathophysiological states. While functional OI can use appropriate and repetitive stimulation paradigms to tease apart global and focal changes, events in pathophysiological monitoring must be sensitive to a single or rare event. Therefore, we consider technological approaches that supply depth resolution to be mandatory. Another issue that should be noted is that strokes affecting deeper structures will not be accessible to the methodology (subcortical infarctions, lacunar stroke and those of the posterior cerebral artery territories). This may apply to roughly 40–50% of all strokes. The limitation of the sensitivity of the method to strokes including the surface of the brain is extremely relevant especially when specific markers in the diseased tissue are targeted. In the adult, depth resolution allows a better differentiation between extra- and intracerebral contributions to the signals measured, but will not yield truly tomographic images of the whole adult brain as has been described in infants [20].

4. Monitoring of (sub)acute stroke

In the (sub)acute phase of ischaemic stroke, after reliable exclusion of haemorrhage, optical ‘brain monitoring’ in the framework of stroke units should ideally serve two goals. It should (i) supply early markers supporting the detection of or ideally preceding clinically apparent deterioration, and (ii) define surrogate markers of the complex pathophysiological sequels of the ischaemic event [70]. The former would tighten the net of surveillance. The standard operating procedures in many stroke units schedule neurological assessment twice daily. However, the disease processes follow a different schedule. Thus, continuous monitoring of oxygenation, perfusion or other parameters available to OI could serve as an alarm to prompt clinical re-evaluation. In this case, sensitivity to changes in haemodynamic parameters is the key feature required, serving as an alarm for repeat clinical evaluation and follow-up neuroimaging to decide on the necessity of a change in the therapeutic regime. To serve the second goal, greater specificity as to the parameter monitored is required. Ideally, a physiological parameter, e.g. tissue oxygenation in the infarcted area, would be continuously available (‘brain oximeter’). This would have the advantage that therapeutic interventions such as modulations in blood pressure, heart rate, glucose and also body temperature and posture could be optimized for their effect on the diseased brain tissue. Ideally, clinicians could rely on a clearly defined normal range for the parameter monitored. As an example, a drop in a well-defined oxygenation index below a
specified value might then be counteracted by raising blood pressure or altering body posture until the parameter returns to the normal range. It is worth noting, however, that the ‘optimal’ tissue oxygenation in subacutely ischaemic tissue is not known, and pathomechanisms not primarily related to haemodynamics, for example, inflammation and apoptosis, are established to contribute to the final volume of infarcted tissue [71,72]. Thus, even pathophysiological monitoring will require large-scale clinical studies to define effective variables for a favourable long-term outcome. Additionally, as yet, OI does not supply absolute values of tissue oxygenation (see §3) and provides more reliable data when it comes to detecting changes of the parameters measured. Therefore, most studies have used procedures that induce a change in haemodynamics or have measured markers of perfusion based on a bolus-tracking approach using ICG in analogy to pwMRI. Since the inter-individual variability of such values may be very large, the value measured over the diseased tissue is often compared with the ‘healthy’ hemisphere, so that the patient serves as his or her own control. If larger arrays of probes were used, a true imaging approach of the surface of the brain might allow a more sophisticated differentiation of tissue at risk and surrounding brain areas.

(a) Monitoring cerebral autoregulation

Measuring TOI over two frontal probes, optimal posture in acute stroke has been investigated [73]. The qualitative analysis \( (n = 7) \) suggests that cerebral oxygenation may decrease in an upright position, an effect that was mostly seen over the affected when compared with the unaffected hemisphere. This may reflect disturbances in autoregulatory capacities in the (sub)acutely ischaemic tissue. Since the alteration was mostly seen over the diseased hemisphere, impairment and potential normalization of autoregulation when assessed by such a simple procedure may serve as a parameter to monitor stroke patients in the (sub)acute stage of the disease.

In a similar approach, changes in CBF were assessed by DCS, which can be easily combined with absorption-based assessment of changes in haemoglobin oxygenation (NIRS) [74]. This exciting new technique has also been applied in stroke patients [69]. Using a standardized protocol applying a \(-5^\circ\) to \(+30^\circ\) head-tilt manoeuvre, 17 acute stroke patients (approx. 2 days after symptom onset) were examined and compared with control subjects with an increased risk for stroke. The flow index obtained by DCS suggests a passive response to the head-tilt position predominantly over the stroke-affected hemisphere. This is in line with the finding of impaired autoregulation in the stroke territory. The high variability of the measurements between subjects is contrasted by a very high reproducibility of the measurements within single subjects on successive days. This strongly suggests that the variability indeed reflects differential pathophysiological states in stroke patients, which may require differential intervention (e.g. posture) in (sub)acute stroke.

Also targeting changes in autoregulation in the diseased tissue after stroke, recent papers explore physiological high-frequency oscillations [75] and discuss the relevance of low-frequency oscillations (LFOs) in patients with carotid artery disease and in the acute phase of stroke [76]. The study by Muehlschlegel et al. [75] analysed the frequency ranges around the cardiac cycle (0.7–3 Hz) and around
the respiratory frequency (0.15–0.7 Hz). The comparison between nine stroke patients and nine age-matched controls showed that the correlation between oscillations in both hemispheres was different in stroke patients when compared with healthy control subjects. Stroke patients showed a larger desynchronization between hemispheres in both frequency ranges, more pronounced in the lower (respiratory) frequency range. The authors suggest that this stems from altered autoregulation in the diseased tissue. It is noteworthy that the approach is simple and allows within-patient comparison (affected versus non-affected hemisphere). Both are definite strengths with regard to a broader application in a clinical setting. However, the underling pathophysiological concept is somewhat unclear, since the assessment of changes in autoregulation in carotid artery stenosis and stroke have been typically described for lower frequencies in the range of 0.1 Hz and below [77–79]. A recent paper [76] reviews the potential of LFOs in stroke and carotid artery disease including studies with transcranial Doppler (TCD) sonography and NIRS. The target pathophysiological phenomenon is an alteration of dynamic cerebral autoregulation. Following the terminology of the large body of literature on ‘vasomotion’, LFOs (approx. 0.1 Hz) and very-low-frequency oscillations (VLFOs) (approx. 0.004 Hz) are differentiated. Oscillations in these frequency ranges are considered not to stem primarily from the rhythmic physiological changes induced by respiration and heart beat (often termed high-frequency oscillations’). Their origin is still largely elusive. Systemic haemodynamics and autonomic (e.g. Mayer waves) but also cerebral generators (e.g. B-waves) must be considered constitutive for their generation and modulation. With regard to their relevance in risk assessment and acute monitoring of stroke, a TCD-derived model [77] predicts that a decrease in phase shift between systemic and cerebral oscillations signals less efficient autoregulation (as proposed for the higher frequency range in the study reviewed above [75]). The review highlights the potential of monitoring phase shifts in the LFO and VLFO as a measure of autoregulation in carotid artery stenosis but potentially also in the penumbra of stroke. For acute ischaemic stroke, the studies measuring cerebral blood flow velocity in the middle cerebral arteries (CBFv-MCA) to correlate them with oscillations in systemic arterial blood pressure (aBP) [80] are somewhat inconclusive. This is potentially due to the fact that very large infarct volumes are required to affect CBFv in the large vessels. The phase changes may be more sensitive to coexisting chronic changes in autoregulation due to carotid stenosis or microangiopathy (see §5). The enhanced sensitivity to focal changes of the oscillations and sensitivity of NIRS to the capillary bed in cortical tissue [58] plus the potential to spatially resolve focal alterations [49] in (sub)acute ischaemia clearly encourage further studies with OI using this approach targeting the penumbra of a cortical infarct.

(b) Monitoring malignant stroke

In malignant stroke, the large infarct volume and the ensuing oedema can lead to brain herniation, which is lethal unless decompression by timely hemicraniectomy is warranted. Malignant stroke is one of the most dramatic complications of stroke, occurring in approximately 10 per cent of MCA infarctions and associated with a mortality of approximately 70 per cent.
A recent study with 24 patients, of whom 13 underwent craniectomy, reports typical patterns of OI parameters [81,82]. Measuring regional oxygen saturation (rSO2), the authors report that the value on admission did not predict outcome. However, the patients who showed a large difference between the rSO2 values of the diseased hemisphere when compared with the ‘healthy’ hemisphere had a better outcome. Also, a narrowing of the interhemispheric rSO2 difference heralded increased swelling, while decompression (by hemicraniectomy) yielded a larger difference in rSO2, with positive values on the infarcted side. While the physiological explanation of increased oxygen saturation (rSO2) on the infarcted side may be surprising, and the assessment of rSO2 values with different monitors has been debated [83,84], the application of oxygenation and CBF parameters by non-invasive OI in patients with malignant stroke seems promising, especially when considering the complicated decision algorithm for invasive therapy [85].

(c) Assessing the efficiency of bypass surgery of cranial vessels

In patients (n = 13) undergoing extra–intracranial anastomosis to prevent imminent stroke due to Moyamoya disease (n = 5) and MCA or internal carotid artery (ICA) (n = 8) occlusion, NIRS was used to test the efficiency of the bypass post-operatively [86]. Compression of the extracerebral feeder of the anastomosis resulted in HbO and HbT decreases in five patients who did not show a declamping effect during the operation. The latter was assessed by visible light spectroscopy (520–580 nm) applied intra-operatively directly over the brain tissue. Although there may be some doubt as to the specificity of these post-operative measurements with NIRS, the paper supplies approximate estimates of the saturation and HbO changes that can be expected in chronically ischaemic (approx. 60%) and revascularized (approx. 90%) brain tissue.

(d) Perfusion assessment by a dye-bolus technique

Targeting perfusion as a monitoring parameter in the (sub)acute phase of stroke, some groups have exploited the option to apply a bolus of ICG. The latency and shape of the increase in absorption due to bolus transit through the sampled tissue yields an indicator of perfusion. A clear advantage of this approach is the magnitude of the optical changes induced by the bolus, clearly detectable even in noisy recordings. The procedure also yields a parameter closely related to mean transit time, which is used to image perfusion in pwMRI. This may be a major strength of the approach, since it allows the merging of a whole brain perfusion ‘snapshot’ at high spatial resolution, supplied by initial pwMRI, with low resolution but, importantly, longitudinal data on the same parameter. The doses typically used allow for pseudo-continuous monitoring. Half-hourly injections of 5 mg ICG result in daily doses far below the recommended maximum and ICG can be considered a sufficiently safe contrast agent [87]. The major issue is extracerebral contamination. Both continuous-wave technology [88] and time-resolved technologies [89,90] have yielded promising results. Studies using either technique showed a clear delay of the arrival of the bolus over the diseased when compared with the non-affected hemisphere, indicating delayed perfusion in the affected territory. A rough correlation with pwMRI has also been demonstrated [91,92]. We deem depth resolution necessary to clearly increase sensitivity to...
Figure 2. Sketch of a potential integration of OI-based monitoring in stroke units. While diagnostic neuroimaging upon admission is mandatory to exclude haemorrhage, subacute monitoring largely targets systemic cardiovascular parameters (ECG, electrocardiogram; aBP, arterial blood pressure; Gluc, blood glucose level; °C, body temperature; etc.). OI might supply (pseudo)continuous readings of various cerebrovascular parameters (perfusion, indexing blood flow; LFO, low-frequency oscillations of HbO/HbR related to autoregulation; rSO2, regional oxygen saturation; etc.). Owing to its comparatively undemanding setup, it could be used as a tool to adjust therapy and potentially warrant follow-up imaging. (Online version in colour.)

the bolus passage in cerebral tissue. This may be afforded by multi-distance approaches (as is currently being tested by our group along the principles of [93]), by frequency-domain [94] and ideally by time-resolved approaches [66]. Options to use ICG fluorescence to enhance sensitivity or assess dye extravasation await further evaluation in a clinical setting [95].

To sum up, OI monitoring in the subacute stage of ischaemic stroke has the potential to fill the gap between high-resolution multimodal assessment of patients as afforded by MRI techniques on admission (dwMRI/pwMRI/MR angiography) and the monitoring of mostly internal-medicine parameters in stroke units (see figure 2). The choice of the parameter depends on its routine applicability and whether the value obtained can be merged with other routine diagnostic procedures. We consider ICG-based perfusion monitoring and measures of dynamic autoregulation most promising in this field.

5. Prevention of stroke in high-risk populations

(a) Intra-operative stroke monitoring

General anaesthesia and any large-scale open surgery bear the risk of intermittent decreases in cerebral oxygenation [96]. This risk is clearly increased during cardiac surgery and carotid artery desobliteration since haemodynamic and thrombembolic strokes can occur intra- and peri-operatively. Intra-operative
monitoring by OI in the latter two groups of patients is clearly the best-studied clinical application of the methodology with regard to ‘brain monitoring’. This is evidenced by studies including several hundred patients. Mostly rSO2 has been the parameter of choice, and studies have defined a clear cut-off value: a drop of more than 20 per cent in this parameter [97] has been shown to be a useful basis on which to devise an algorithm to counteract the risk of cerebrovascular injury [98]. A number of excellent reviews have discussed the validity of intra-operative monitoring using OI, with somewhat diverging conclusions ranging from modest to clear evidence that it is useful [99–101]. Although the superiority of OI compared with ‘established’ electrophysiological or TCD monitoring is hotly debated—e.g. for the decision on shunting during carotid endarterectomy (CEA) [102]—intra-operative monitoring by OI has clearly reached the clinic. Considering the fact that most of the studies used rather simple commercial monitors, application of state-of-the-art technology is highly advisable and may significantly increase specificity [103]. Also, sensitivity can be enhanced by using true imaging approaches as opposed to single-channel devices, as well demonstrated in a case report on a watershed infarction during CEA [104].

Outside the operating theatre, vasospasm bears the risk of secondary ischaemic stroke after a subarachnoid haemorrhage. The option to monitor patients in this phase of the disease has been investigated by a number of smaller-scale studies. Parameters investigated include rSO2 [105], TOI with regard to autoregulation [106], time-resolved absolute quantification methods [107] and ICG-based perfusion assessment [108]. Beyond the monitoring of cerebral oxygenation to prevent stroke in high-risk scenarios during surgery and on neurointensive care units, a number of studies have investigated the potential of OI in ambulatory risk populations.

(i) Chronic vasculopathy: micro- and macroangiopathy

Microangiopathy may result in stroke, but is also an established aetiology of vascular dementia. It was demonstrated that NIRS is able to show a reduction of hypercapnia-induced vasomotor reactivity (VMR) in patients \((n = 46)\) with cerebral microangiopathy [109]. The alteration in VMR correlated with the severity in white matter lesions in this patient sample. The sensitivity and specificity were higher when VMR alteration was assessed by NIRS (HbO, HbR, HbT) compared with the assessment by TCD of the MCAs. A recent follow-up study compared patients with vascular and neurodegenerative dementia [110]. Patients with multi-infarct dementia were deliberately excluded and VMR was assessed in patients with probable Alzheimer’s disease and patients who were diagnosed with possible vascular dementia \((n = 17\) for each group). The results show that VMR (as measured by TCD) is impaired in both conditions when compared with age-matched and young control subjects. Interestingly, the NIRS parameters (HbO and HbDiff \(=\) HbO – HbR) showed a significant alteration in the hypercapnia reaction only in the vascular dementia group. A partial normalization of the VMR is reported after treatment with galantamine, putatively due to the cholinergic contribution to cerebrovascular autoregulation. A similar rationale is behind a study by Schroeter and colleagues, who investigated spontaneous LFOs and the haemodynamic response magnitude to visual stimulation [111]. They showed that alteration of both
vascular parameters correlated well with cognitive function in 14 patients with microangiopathy. A follow-up study reproduced these findings for a Stroop task assessing frontal lobe function in patients with microangiopathy and healthy controls [112].

A less demanding alternative to hypercapnia-based assessment of cerebral autoregulation has been proposed. Spontaneous LFOs of approximately 0.1 Hz can be recorded in arterial blood pressure (aBP), in blood flow velocity (CBFv) in the large cerebral arteries [113] and in the oxygenation parameters (HbO and HbR) [78–79,114,115]. The phase lag between aBP and CBFv has been used as an indicator of alterations in cerebral autoregulation. Using a forced 0.1 Hz breathing task combined with non-invasive assessment of aBP, CBFv and NIRS parameters in patients with unilateral carotid stenosis (n = 28) and age-matched controls (n = 38) showed changes in the phase shift between aBP and NIRS parameters as well as CBFv. This is in line with impaired dynamic autoregulation on the side of the stenosis [116]. Interestingly, the phase shift between HbO and HbR was also significantly increased on the affected compared with the unaffected hemisphere in patients. Thus, even without multimodal assessment, NIRS may provide a measure of cerebral autoregulation. With regard to an even broader population at a potentially increased risk of stroke, a recent paper [117] elegantly showed that, during sleep, brain oxygenation is altered in patients suffering from different kinds of breathing disorders (total n = 19). In severe obstructive apnoea, an increase in HbR and decrease in HbO was seen during the apnoea events, while mild hypopnoea was associated with the inverse pattern. This may be an important finding for further elucidating the pathophysiological basis of the increased risk for stroke in patients with sleep apnoea.

To sum up, we are convinced that OI can successfully contribute to intraoperative monitoring during surgery with high risk of stroke. Here, the major challenge is to supply devices that are more selective with regard to intracerebral oxygenation and haemodynamic changes and ideally monitor more than frontal lobe oxygenation (i.e. provide images of larger parts of the brain’s surface). In intensive care units, cerebral oxygenation monitoring may be beneficial and largely follows the same principles as discussed in the previous section with regard to stroke units. The assessment of vascular reactivity (autoregulation and stimulation-evoked responses) in ambulatory high-risk populations may largely be of clinical-scientific interest. However, in concert with other neuroimaging techniques, this may elucidate important pathophysiological principles as discussed with regard to differences and commonalities between degenerative and vascular dementia.

6. Rehabilitation

Applications in (sub)acute stroke monitoring and prevention of stroke in high-risk populations target the integrity of cerebral haemodynamics. The potential of OI to map functional activation comes into play when investigating neuroplasticity accompanying recovery from and/or compensation for deficits. This field is based on the large body of functional activation studies in healthy volunteers [118,119]. One very important general caveat, however, is the fact that the basis of the

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imaging signal itself, the vascular response, may be altered owing to stroke and/or underlying vascular pathology, which is targeted during acute monitoring and prevention.

(a) Alteration of vascular response to functional stimulation after stroke

This potential alteration of the vascular response in stroke patients has been explicitly addressed by a series of studies using OI. In patients with MCA or ICA occlusion ($n = 6$; approx. 5 months post-stroke), the oxygenation response to a simple motor paradigm has been compared with age-matched controls [120]. In the patients, a ‘paradoxical’ increase in HbR is reported, correlating well with the absence of a reliable blood oxygen level-dependent (BOLD) contrast increase as assessed by functional magnetic resonance imaging (fMRI) (see figure 3a). Such alterations seem to depend on the severity of the haemodynamic compromise, which may be dynamic in the early phase of stroke. Thus, alterations in the vascular response need to be considered so as not to be confounded with changes reflecting functional plasticity. In this vein, the group investigated 10 patients with subacute MCA territory stroke. Indeed, oxygenation response was strongly influenced by the degree of perfusion deficit (as independently measured by single-photon emission computed tomography). In normal controls and mild hypoperfusion, the response pattern showed the typical focal hyperoxygenation ($\text{HbO} \uparrow$ and $\text{HbR} \downarrow$). In contrast, very low perfusion resulted in an inverted HbR($\uparrow$) response, which was also reflected in the decreased BOLD signal in fMRI [122,123]. Recently, data reported by the group in five patients suggest that the inverse HbR response may be abolished after revascularization [124]. We believe that OI is a valuable tool in this field, allowing independent assessment of vascular response integrity, which is crucial for plasticity research with fMRI after stroke. Such approaches, especially when combining OI and fMRI [125,126], may profit from additional parameters supplied by OI (HbO, HbT).

(b) Investigation of functional plasticity in chronic stroke

Beyond basic issues of neurovascular coupling in the diseased brain, OI has clear advantages over fMRI with regard to ‘real-world’ assessment [127] of functional reorganization and can detect activation patterns in response to typical clinical rehabilitation procedures [128]. To examine the adaptive changes in the cortical contribution to gait control, the group of Kubota and co-workers established a treadmill setup allowing the assessment of cortical activation during normal gait [121,129] (figure 3b). Notably, gait disturbance is one of the key functional deficits in stroke, but is not accessible to fMRI investigation. In patients suffering from infratentorial stroke ($n = 12$), the group neatly demonstrated that compensation for the automatic gait control may cause a sustained prefrontal activation ($\text{HbO} \uparrow$) in these patients when compared with an age-matched control group [130]. In the latter, prefrontal hyperoxygenation decreased during the steady state of gait, while patients with gait disturbances showed sustained activation in the prefrontal cortex. In patients suffering from severe gait disturbance due to hemiplegia caused by large MCA infarctions, differential activations were demonstrated for different therapeutic strategies to assist treadmill walking [131].

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Figure 3. Applications of OI in the context of plasticity research after stroke. (a) Functional neuroimaging in cerebrovascular disease needs to acknowledge that the imaging signal, i.e. the vascular response, may be altered. The example shows that, after stroke, the HbR response to a motor stimulation can be inverted in the post-ischaemic tissue (upper graphs). This also explains why no BOLD contrast increase is seen in the fMRI (lower right graph) performed in the same patient. (Adapted from Murata et al. [120]. Reproduced by permission.) (b) Tasks that cannot be examined by fMRI may be of great importance to rehabilitation: an example of imaging gait control by OI. (Adapted from Miyai et al. [121]. Reproduced by permission.) (c) Brain–computer interfaces may allow automated adaptive rehabilitation programmes. OI can be combined with EEG to supply markers of brain activation, which—converged with performance assessment by, for example, data gloves—could shape the training task. This shaping could be supervised by an expert (therapist, MD). (Online version in colour.)

With regard to upper extremity control after stroke, a small study (n = 5) used a hand grip task while cortical oxygenation changes were monitored in patients who suffered from hemiparesis due to small-size MCA infarcts. Compared with normal controls and to performance in the unaffected hand, the pattern of activation (HbO↑ and slight HbR↓) was strongly bilateral for patients for unilateral hand movements of the affected side. Interestingly, a shift to a more contralateral pattern was seen in the longitudinal control examination after more than a month had elapsed post-stroke [132]. This extends the earlier findings of OI sensitivity for an altered functional organization in the motor system after stroke. Using a hand grip task, hemiparetic patients showed increased
ipsilateral motor-cortex activation during performance on the affected side. The results largely correlated with fMRI findings in the same patients/volunteers [133]. A case study documenting changes in a hand grip task over the course of a two week constraint-induced therapy scheme should be mentioned since it highlights the potential of multimodal assessment by converging results of fMRI, OI and transcranial magnetic stimulation based cortical mapping with the outcome. With regard to the OI results, a ‘laterality index’ increased, potentially signalling normalization of the functional organization of the motor cortices [134]. Another study investigated electromyography-triggered electrical muscle stimulation (functional electrical stimulation) in patients after stroke. Beyond the partial success of the approach, a larger haemodynamic response (oxy-Hb↑) was seen over the motor cortex. This finding may reflect some facilitation of the lesioned motor system [135]. Taking this idea one step further, a recent study [136] reports the first promising results of a brain–computer interface application in rehabilitation using OI. When cerebral oxygenation exceeded a threshold in volunteers, 50Hz electrical stimulation was applied to target arm muscles.

This leads to the question of what the perspectives for OI after stroke are. Clearly, a better and more detailed understanding of plasticity in lesioned cortical networks requires a multimodal approach based on MRI techniques supplying spatially refined and multidimensional data (structural: voxel-based morphometry (VBM), diffusion tensor imaging (DTI); and functional: resting state connectivity and evoked activation using BOLD contrast). However, many tasks may require portable tools to investigate brain activation. Here, OI in combination with EEG has a great potential, as discussed in the literature on brain–computer interfaces [47,137–139]. Simultaneous assessment of EEG parameters including both event-related potentials [140] and also task-related (de)synchronization of the rhythmic electrophysiological activity [141–143] can serve two goals: it can provide an independent indicator of brain function with very high temporal resolution; and it may also allow the testing of the integrity or alteration of neurovascular coupling in patients with cerebrovascular pathology. Such approaches could eventually truly assist rehabilitation, since feedback methods, or adaptive increase of training level (‘shaping’), would allow additional or therapist-guided at-home training (figure 3c).

7. Problems and perspectives

The many promising approaches reviewed in this paper may raise the question of why non-invasive optical methods have as yet not been introduced into routine clinical care for stroke patients. We will therefore briefly highlight the major obstacles and potential avenues to overcome them to allow a critical appraisal of the perspective of the methodology. Starting at the patient’s head, one seemingly trivial problem is how optical probes are fixed to reach a compromise between patient comfort and stability of the recording. This becomes evident in the fact that the clinically most successful application (i.e. intra-operative monitoring) has been reached in anaesthetized and immobilized patients. The number of types of headgear developed may equal the number of groups in the field. There is, however, a clear need for professional development of, for example, caps with integrated optical probes allowing fast and comfortable montage of a larger array of
probes. To avoid the increase in bulkiness, especially when targeting large arrays to achieve whole-head coverage, prototypes of wireless light-emitter and -detector caps have been probed but will need to be made available to clinical users.

The next key question is whether either the technically rather undemanding continuous-wave technology or time-domain monitors are needed. We believe that, especially for the assessment of pathophysiological state-dependent variables such as perfusion, spontaneous LFOs and absolute values of tissue oxygenation, time-resolved techniques are mandatory. Their potential to reach a coarse depth resolution is the prerequisite to exclude the possibility that changes in any of these parameters are mimicked by changes in systemic blood pressure or posture altering extracerebral haemodynamics. Once such data are acquired, their analysis relies on a number of strong assumptions. The number of models proposed to quantify changes in oxygenation is large. This may be justified, respecting the many theoretical challenges pertaining to light propagation in highly scattering media (i.e. biological tissue); however, to reach the clinical user, a jointly developed standard analysis is clearly needed. This would allow a comparison between results of different studies and different research groups. Finally, but also importantly, the future of the field will depend on how efficient a cooperation can be reached between technologists, theoreticians and pathophysiologists to motivate clinicians to conduct larger-scale trials in well-defined patient cohorts with an open outcome.

Although the tasks to be tackled represent a tremendous challenge, we believe they are worthwhile, considering the fact that a methodology allowing pathophysiologically motivated brain monitoring will greatly improve care for stroke patients, especially in the subacute stage of the disease.

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