Intrinsic optical imaging

Intrinsic signal optical imaging is a functional imaging modality where the reflectance of red light indicates active portions of cortex, as developed by Grinvald et al. is a powerful technique for monitoring neural function in the in vivo central nervous system. The advent of this dye-free imaging has also enabled us to monitor human brain function during neurosurgical operations.

It offers advantages for studying functional organization in the cat or monkey visual cortex and the rodent somatosensory (whisker barrel) cortex.

In intrinsic optical signals, it is indicated that there are at least three components.

The first component originates from activity-dependent changes in the oxygen saturation level of hemoglobin. The second component originates from changes in blood volume that are probably due to dilation of venules in an area containing electrically active neurons. The third component arises from light-scattering changes that accompany cortical activation caused by ion and water movement, expansion and contraction of extracellular spaces, capillary expansion or neurotransmitter release.

The intrinsic optical imaging technique was also applied to the human brain during neurosurgery. Haglund et al. first demonstrated the usefulness of this technique for functional localization in the human brain. They obtained maps during stimulation-evoked epileptiform afterdischarges and cognitively evoked functional activity. Functional images induced by language tasks were also shown by Cannestra et al. and Pouratian et al. they detected neuronal responses from the Broca's and Wernicke's areas in awake patients.

There are a few reports of intrinsic optical imaging from the human somatosensory cortex in response to median/ulnar nerve stimulation or digit stimulation. Although these reports showed neural responses in the primary somatosensory cortex, they did not separate optical responses among the Brodmann's subdivisions.

Intrinsic optical signal (IOS) imaging, laser speckle flowmetry (LSF) and electrocorticography were performed in different configurations in three groups of in total 18 swine. SDs were elicited by topical application of KCl or occurred spontaneously after middle cerebral artery occlusion. Movement artefacts in IOS were compensated by an elastic registration algorithm during post-processing. Using movement-compensated IOS, we were able to differentiate between four components of optical changes, corresponding closely with haemodynamic variations measured by LSF. Compared with ECoG and LSF, our setup provides higher spatial and temporal resolution, as well as a better signal-to-noise ratio. Using IOS alone, we could identify the different zones of infarction in a large gyrencephalic middle cerebral artery occlusion pig model. We strongly suggest movement-compensated IOS for the investigation of the role of haemodynamic responses to SDs during the development of secondary brain damage and in particular to examine the effect of potential therapeutic interventions in gyrencephalic brains [1)].

In a study, using intraoperative optical imaging of intrinsic signals (iOIS) recording techniques,

detailed cortical activations within the auditory cortex in response to auditory and somatosensory stimulation were recorded from three intraoperative anesthetized patients with brain tumor located at superior temporal gyrus.

At both green-light (545±13 nm) and red-light (610±10 nm) illumination, the primary and secondary auditory cortices showed to be respond significantly to the somatosensory stimulation. As induced by the somatosensory stimulus, the average overlapping rate of the activated region was 74.51% ± 0.15%, and the peak responding time occurred at post-stimulus 7-8 seconds. In addition, there was no significant difference of the peak responding time between auditory and somatosensory stimuli ($P<0.01$, paired t-test).

These findings provide novel evidence for multisensory interplay within human auditory cortex at early stage of cortical processing, which extends the understandings of multisensory mechanism of human brain functions [2)]

Usefulness of Intraoperative Intrinsic Optical Imaging for Neurosurgery

Intraoperative optical imaging (IOI) is an experimental technique used for visualizing functional brain areas after surgical exposure of the cerebral cortex. This technique identifies areas of local changes in blood volume and oxygenation caused by stimulation of specific brain functions.

Sato et al briefly describe his own experience in functional mapping of the human somatosensory cortex, carried out using intraoperative optical imaging. The maps obtained demonstrate new additional evidence of a hierarchy for sensory response patterns in the human primary somatosensory cortex [3)].

They performed intrinsic optical imaging of neuronal activity induced by peripheral stimulation from the human primary somatosensory cortex during brain tumor surgery for 11 patients. After craniotomy and dura reflection, the cortical surface was illuminated with a xenon light through an operating microscope. The reflected light passed through a bandpass filter, and they acquired functional images using an intrinsic optical imaging system. Electrical stimulation of the median nerve, or the first and fifth digits, induced biphasic intrinsic optical signals which consisted of a decrease in light reflectance followed by an increase. The decrease in light reflectance was imaged, and we identified a neural response area within the crown of the postcentral gyrus. In experiments on first and fifth digit stimulation, we identified optical responses in separated areas within the crown of the postcentral gyrus, i.e. near the central sulcus and near the postcentral sulcus. In the former response area, separate representations of the two fingers were observed, whereas in the latter response area, the two fingers were represented in the same region. A similar somatotopic representation was observed with electrical stimulation of the first and third branches of the trigeminal nerve. These results seem to support the hypothesis of hierarchical organization in the human primary somatosensory cortex [4)].

In 14 patients with tumors adjacent to or within the sensorimotor cortex, intrinsic optical signals in response to somatosensory stimuli were recorded by illuminating the brain surface with Xe white light and imaging the reflected light passing through a bandpass filter (605 nm). Results were compared with intraoperative recordings of sensory evoked potentials in all 14 patients and with noninvasive

mapping modalities such as magnetoencephalography and positron emission tomography in selected patients. In all but two patients, the somatosensory optical signals were recorded on the primary sensory cortex. Optical signals elicited by stimulation of the first and fifth digits and the three branches of the trigeminal nerve were recorded at different locations on the sensory strip. This somatotopic information was useful in determining the resection border in patients with glioma located in the sensorimotor cortex. [5].

Meyer et al implement an easy-to-use and robust imaging setup that can be used in clinical routine with standard hardware equipment (surgical microscope, high-resolution camera, stimulator for peripheral nerve stimulation) and custom-made software for intraoperative and postoperative data analysis. Evaluation of different light sources (halogen, xenon) showed a sufficient temporal behavior of xenon light without using a stabilized power supply. Spatial binning (2×2) of the camera reduces temporal variations in the images by preserving a high spatial resolution. The setup was tested in eight patients. Images were acquired continuously for 9 min with alternating 30-s rest and 30-s stimulation conditions. Intraoperative measurement and visualization of high-resolution two-dimensional activity maps could be achieved in <15 min. The detected functional regions corresponded with anatomical and electrophysiological validation. The integration of optical imaging in clinical routine could successfully be achieved using standard hardware, which improves guidance for the surgeon during interventions near the eloquent areas of the brain [6].

In 41 patients with tumor lesions adjacent to the postcentral gyrus, lesions were surgically removed by using IOI during stimulation of the contralateral median nerve. Optical properties of the cortical tissue were measured with a sensitive camera system connected to a surgical microscope. Imaging was performed by using 9 cycles of alternating prolonged stimulation and rest periods of 30 seconds. Intraoperative optical imaging was based on blood volume changes detected by using a filter at an isosbestic wavelength ($\lambda = 568$ nm). A spectral analysis algorithm was used to improve computation of the activity maps. Movement artifacts were compensated for by an elastic registration algorithm. For validation, intraoperative conduction of the phase reversal over the central sulcus and postoperative evaluation of the craniotomy site were used.

The new method and analysis enabled significant differentiation ($p < 0.005$) between functional and nonfunctional tissue. The identification and visualization of functionally intact somatosensory cortex was highly reliable; sensitivity was 94.4% and specificity was almost 100%. The surgeon was provided with a 2D high-resolution activity map within 12 minutes. No method-related side effects occurred in any of the 41 patients.

Sobottka et al., approach makes IOI a contact-free and label-free optical technique that can be used safely in a routine clinical setup. Intraoperative optical imaging can be used as an alternative to other methods for the identification of sensory cortex areas and offers the added benefit of a high-resolution map of functional activity. It has great potential for visualizing and monitoring additional specific functional brain areas such as the visual, motor, and speech cortex. A prospective national multicenter clinical trial is currently being planned [7].

Complete removal of epileptogenic cortex while preserving eloquent areas is crucial in patients undergoing epilepsy surgery. In this manuscript, the feasibility was explored of developing a new

methodology based on dynamic intrinsic optical signal imaging (DIOSI) to intraoperatively detect and differentiate epileptogenic from eloquent cortices in pediatric patients with focal epilepsy. From 11 pediatric patients undergoing epilepsy surgery, negatively-correlated hemodynamic low-frequency oscillations (LFOs, ~ 0.02-0.1 Hz) were observed from the exposed epileptogenic and eloquent cortical areas, as defined by electrocorticography (ECoG), using a DIOSI system. These LFOs were classified into multiple groups in accordance with their unique temporal profiles. Causal relationships within these groups were investigated using the Granger causality method, and 83% of the ECoG-defined epileptogenic cortical areas were found to have a directed influence on one or more cortical areas showing LFOs within the field of view of the imaging system. To understand the physiological origins of LFOs, blood vessel density was compared between epileptogenic and normal cortical areas and a statistically-significant difference ($p < 0.05$) was detected. The differences in blood-volume and blood-oxygenation dynamics between eloquent and epileptogenic cortices were also uncovered using a stochastic modeling approach. This, in turn, yielded a means by which to separate epileptogenic from eloquent cortex using hemodynamic LFOs. The proposed methodology detects epileptogenic cortices by exploiting the effective connectivity that exists within cortical regions displaying LFOs and the biophysical features contributed by the altered vessel networks within the epileptogenic cortex. It could be used in conjunction with existing technologies for epileptogenic/eloquent cortex localization and thereby facilitate clinical decision-making [8].

1)

Schöll MJ, Santos E, Sanchez-Porras R, Kentar M, Gramer M, Silos H, Zheng Z, Gang Y, Strong AJ, Graf R, Unterberg A, Sakowitz OW, Dickhaus H. Large field-of-view movement-compensated intrinsic optical signal imaging for the characterization of the haemodynamic response to spreading depolarizations in large gyrencephalic brains. J Cereb Blood Flow Metab. 2016 Sep 27. pii: 0271678×16668988. [Epub ahead of print] PubMed PMID: 27677673.

2)

Zhou Q, Wang Y, Yi L, Tan Z, Jiang Y. Multisensory interplay within human auditory cortex: new evidence from intraoperative optical imaging of intrinsic signal. World Neurosurg. 2016 Oct 26. pii: S1878-8750(16)31089-0. doi: 10.1016/j.wneu.2016.10.100. [Epub ahead of print] PubMed PMID: 27794511.

3)

Sato K, Nariai T, Momose-Sato Y, Kamino K. Intraoperative intrinsic optical imaging of human somatosensory cortex during neurosurgical operations. Neurophotonics. 2017 Jul;4(3):031205. doi: 10.1117/1.NPh.4.3.031205. Review. PubMed PMID: 28018935.

4)

Sato K, Nariai T, Sasaki S, Yazawa I, Mochida H, Miyakawa N, Momose-Sato Y, Kamino K, Ohta Y, Hirakawa K, Ohno K. Intraoperative intrinsic optical imaging of neuronal activity from subdivisions of the human primary somatosensory cortex. Cereb Cortex. 2002 Mar;12(3):269-80. PubMed PMID: 11839601.

5)

Nariai T, Sato K, Hirakawa K, Ohta Y, Tanaka Y, Ishiwata K, Ishii K, Kamino K, Ohno K. Imaging of somatotopic representation of sensory cortex with intrinsic optical signals as guides for brain tumor surgery. J Neurosurg. 2005 Sep;103(3):414-23. PubMed PMID: 16235671.

6)

Meyer T, Sobottka SB, Kirsch M, Schackert G, Steinmeier R, Koch E, Morgenstern U. Intraoperative optical imaging of functional brain areas for improved image-guided surgery. Biomed Tech (Berl). 2013 Jun;58(3):225-36. doi: 10.1515/bmt-2012-0072. PubMed PMID: 23729529.

7)

Sobottka SB, Meyer T, Kirsch M, Koch E, Steinmeier R, Morgenstern U, Schackert G. Intraoperative optical imaging of intrinsic signals: a reliable method for visualizing stimulated functional brain areas during surgery. J Neurosurg. 2013 Oct;119(4):853-63. doi: 10.3171/2013.5.JNS122155. PubMed PMID: 23790114.

8)

Song Y, Riera JJ, Bhatia S, Ragheb J, Garcia C, Weil AG, Jayakar P, Lin WC. Intraoperative optical mapping of epileptogenic cortices during non-ictal periods in pediatric patients. Neuroimage Clin. 2016 Feb 26;11:423-34. doi: 10.1016/j.nicl.2016.02.015. PubMed PMID: 27104137; PubMed Central PMCID: PMC4827725.