Executive Summary:

The NEUROPT project aimed at the development and clinical validation of advanced non-invasive optical methodologies for in-vivo diagnosis, monitoring, and prognosis of major neurological diseases (stroke, epilepsy, ischemia), based on diffuse optical imaging by pulsed near infrared light.

Established diagnostic imaging modalities (e.g. X-ray Computed Tomography, Magnetic Resonance Imaging, Positron Emission Tomography) provide 3D anatomical, functional or pathological information with spatial resolution in the millimetre range. However, these methods cannot be applied continuously or at the bedside. Diffuse optical imaging provides a valuable complementing tool to assess perfusion and blood oxygenation in brain tissue and their time evolution in a continuous or quasi-continuous manner. The devices are portable and comparably inexpensive and can be applied in adults and in children.

Time-domain techniques are acknowledged as offering superior information content and sensitivity compared to other optical methods and the main advantages of the use of the time-resolved techniques are:

- the ability to provide depth-selective signals (in particular variance and of the time-of-flight distribution and early vs. late time gating of the time-of-flight distribution) which allow to eliminate or at least to greatly suppress the contamination of near-infrared spectroscopy (NIRS) signals by superficial tissues (skin, scalp);
- the ability to differentiate between the effects of scatter and those of absorption;
- the ability to suppress motion artefacts which are often present in patients who show involuntary movements. The consequences are better quantification of physiological parameters (e.g. blood volume and oxygenation), improved spatial resolution, and overall robustness of the NIRS measurements.

The consortium achieved major developments in technology and data analysis that will enhance time-domain diffuse optical imaging with respect to spatial resolution, sensitivity, robustness of quantification as well as performance of related instruments in clinical diagnosis and monitoring.

The diagnostic value of time-domain diffuse optical imaging have been assessed by clinical pilot studies addressing specific neurological disorders, in comparison with established neurophysiological and neuroimaging techniques. In particular the comparison of NIRS with electroencephalography (EEG) data, revealed significant convergences of temporal and topographical patterns. Comparison of multimodal procedures performed in patients with cortical hyperexcitability (sustaining cortical myoclonus), including EEG, NIRS, functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) assisted by neuronavigation, gave rise to coherent results. The location of hemodynamic changes, revealed by NIRS and fMRI, largely overlapped. In acute stroke patients, the difference between the ICG bolus latency in the diseased compared to the undiseased hemisphere showed an effect very compatible with the clinically expected perfusion delay by means of perfusion weighted MR imaging (pwMRI).

Perspectives regarding clinical application of time-domain diffuse optical brain imaging have been estimated and a reliable basis for a potential commercialisation of this novel technique by European system manufacturers has been created. Larger application in patient series of the newly implemented NIRS technologies will sustain a larger and more selective application, namely in patients with acute disease implicating dominant hemodynamic impairment.

Project Context and Objectives:

Neuroradiological techniques have vastly influenced our understanding of diseases such as stroke, multiple sclerosis and epilepsy. Computed Tomography, Magnetic Resonance Imaging and Positron Emission Tomography provide a cornucopia of anatomical and physiological data which help to guide diagnosis and therapy in clinical practice. However, in the course of highly dynamic brain diseases such as acute stroke and epilepsy the diseased brain remains most of the time unmonitored. Even intensive care units specialized for neurological diseases essentially monitor systemic parameters, such as heart rate or blood pressure. Specific neurological monitoring techniques like intracranial pressure assessment and microdialysis require surgical intervention. Electroencephalography, a technique established some 80 years ago, stands alone in its ability to continuously and non-invasively monitor the brain. Our proposal is therefore motivated by the ambition to provide a clinical tool for continuous monitoring of the haemodynamic parameters cerebral oxygenation and perfusion. This tool should be compatible with existing neuro-monitoring techniques (EEG, Doppler ultrasound) and complement conventional (non-continuous) neuroimaging methods (MRI/CT/PET).

The present proposal aims at the development and clinical validation of advanced non-invasive optical brain imaging. This methodology will be applicable in the acute stage of major neurological diseases, including stroke, hypoxic-ischaemic encephalopathy, and epilepsy. It can be used at the bedside, and is portable, safe, and inexpensive. This technique potentially provides information on clinically valuable parameters such as perfusion and blood oxygenation with a temporal resolution sufficient to promptly determine unfavourable changes in the brain state. It allows simultaneous registration with electrophysiological monitoring by electroencephalography (EEG) and can be easily combined with transcranial Doppler sonography. Finally, as it has been demonstrated in functional studies, optical measurements can be performed simultaneously during MRI or PET imaging. Thus it is feasible to integrate a facility for continuous, low spatial resolution monitoring with systems which provide high spatial resolution 'snapshots' of pathophysiological processes. In short, optical methods are expected to become a complementary monitoring tool in neurological intensive care (e.g. stroke units) and during diagnostic observation in paroxysmal events (e.g. epileptic seizures). The central task of this proposal is to accomplish the transfer of a promising technique into routine clinical practice.

The concerted program of work proposed here has been designed to address the most critical issues which have so far hindered widespread application of optical techniques to brain monitoring and imaging. The present limitations of optical techniques can be considered to be poor spatial resolution, artefacts caused by extra-cerebral contribution, and a lack of absolute quantification of physiological parameters. The core activities of this proposal are focussed on substantial developments in time-domain imaging and spectroscopy. The unsurpassed level of expertise of the European groups involved in this area is recognized worldwide. Time-resolved techniques are acknowledged as offering superior information content and sensitivity compared to other optical methods, allowing for separation between the contributions of surface tissues (e.g. skin and skull) and brain tissue. Time domain imaging can also differentiate between the effects of scatter and those of absorption. The consequences are better quantification of physiological parameters (e.g. blood volume and oxygenation) and improved spatial resolution.

The time-domain technology is based on sources of ultrafast (picoseconds or shorter) near-infrared pulses, fast photon counting detectors, and time-of-flight measurement electronics. The timeliness of this proposal stems in part from the recently emerging new technologies which will make the time-domain approach considerably more competitive in terms of signal quality, simplicity of use, cost, and portability. This project will involve exploiting new technological advances while also implementing and validating a number of novel methodological ideas, such as the 'null-distance', the 'dense topographic', and the 'multi-spectral' approaches. The overall goal of the consortium is to achieve the breakthrough of an effective

clinical diagnostic methodology by advancing the basic technological approach in a concerted manner. A major synergistic effect will be accomplished by the close interaction between commercial developers of new photonic technology, researchers who are experienced in devising time-resolved systems for medical applications, experts in the development of dedicated methods of data analysis, and groups of clinicians and scientists who are engaged in challenging diagnostic applications of the new technologies.

Objectives:

The major objectives were as follows:

Objective 1

Development of novel methodologies for optical imaging of the brain, yielding improved spatial resolution, widespread coverage of the head, optimum selectivity to signals from the brain, and absolute quantification of physiological data. In particular, a novel 'null source-detector separation' approach, a 'dense topography' approach, and a 'multi-spectral' approach will be pursued. These developments will exploit the following technological advances offered by the participating SMEs within the project:

- Picosecond fibre laser supercontinuum sources with high spectral brightness in the wavelength interval from 600 nm to 900 nm;
- Single-photon avalanche diode detectors with comparatively large area and ultra-fast time-gating electronics;
- Time-correlated single photon counting electronics with multi-channel capability in conjunction with high data acquisition rates.

This work will be accompanied by parallel developments in modelling of pulsed near-infrared light propagation in the brain. By solving the inverse problem, the improvements in modelling will lead to better lateral and depth resolution, localisation, and quantification of optical properties within various tissue compartments of the head and brain.

The objective will be considered achieved if the novel methodologies produce significant improvement in spatial resolution, sensitivity, quantification of optical properties, both on simulated data and on measurements of heterogeneous tissue phantoms (month 24).

Milestone M4: 'Evaluation of novel approaches and methodologies for time-domain diffuse optical imaging'.

Objective 2

Development of new time-domain systems for diffuse optical imaging of the brain (clinical prototypes), exploiting the improved features offered by the novel approaches, and adapted to the needs of specific clinical applications in neurological assessment. The important factors are:

- Compliance with national and/or European regulations on the use of medical devices for clinical evaluation;
- Development of suitable optical fibre probes or helmets which maximise comfort for the patients;
- Ease of operation of the instruments in a clinical setting.

Milestone M2: Upgrade of existing time-resolved systems (month 12).
Milestone M5: New instruments based on novel approaches and methodologies available for clinical measurements (month 36).

Objective 3

- Characterisation of performance of instruments together with basic methods of data analysis.
- Definition and implementation of standardised protocols for the quality assessment of instruments (month 36).

- Support for Milestones M2 and M5.

Objective 4

Assessment of the diagnostic value of time-domain brain imaging by clinical pilot studies which address several major neurological pathologies. A common feature will be the long term stability of measurements and the potential to co-register vascular and electrophysiological changes simultaneously in patients. We deliberately choose to include both cerebrovascular conditions (stroke, haemorrhage, hypoxia) and 'neuronal' conditions (epilepsy, myoclonus, dystonia) to highlight the current interest in the respective complementary monitoring modality. Specifically we will perform pilot studies to investigate:

- Epilepsy, cortical myoclonus, movement disorders: long-term monitoring of haemodynamic processes preceding and accompanying seizures;
- Acute stroke: mapping and long-term monitoring of blood oxygenation in brain tissue; assessment of perfusion by bolus tracking of the optical contrast agent indocyanine green (ICG);
- Brain hemorrhage: mapping of changes in oxy- and deoxy-haemoglobin concentrations in the brain, and assessment of perfusion by ICG bolus tracking;
- Hypoxic-ischaemic brain injury and haemorrhage in newborn infants: whole-brain images of blood volume, oxygenation, and scattering properties.

Milestone M1: Definition and harmonisation of protocols and approval by Ethic Committees (month 6).

Milestone M3: Feasibility of long-term measurements with time domain imaging systems. Co-registration with EEG (month 24).

Following completion of the clinical pilot studies, the prospects for widespread clinical application of time-domain optical brain imaging and spectroscopy will be evaluated. Our final results will also provide the means for potential European systems manufacturers to assess the likely prospects for commercialisation of the novel technique.

Milestone M4: Evaluation of novel approaches and methodologies for time-domain diffuse optical imaging (month 24).

Milestone M6: Evaluation of the diagnostic value of time-domain diffuse optical imaging and spectroscopy of the brain (month 48).

Project Results:

WP1 Novel strategies for time-domain diffuse optical imaging of the brain

Start month: 1
End Month: 36
WP Leader: P1A PoliMi_FIS

Task 1.1: Null source-detector separation approach

Previous theoretical investigations have shown that the use of short source-detector (interfibre) distance in time-domain diffuse optical imaging yields better contrast, spatial resolution, and higher signal as compared to large interfiber distances. This concept was explored using Single-Photon Avalanche Diodes (SPAD) operated in fast-gated mode and developed within WP2. An extensive study performed both on simulations and phantom measurements aimed at understanding the system behaviour and to optimize the overall performances. The time-gated SPAD regime was described by a non time-invariant operator (Spread Matrix), yielding the temporal spreading of information caused by the physical detector, related both to the rising edge of the gate, and to the diffusing decay tail of the SPAD. Furthermore, a new phenomenon, termed 'Memory Effect' was identified, leading to an increase in background level, ultimately responsible for the maximum dynamic range of the device. These findings led to the optimization of the design of the system, with the implementation of a 100 nanometres diameter SPAD with a decay tail <100 ps, and enabling a dynamic range in excess of 7 decades.

Two laboratory workstations were developed in Milan and in Berlin, in joint collaboration between PoliMi_FIS, MPD, PTB, Fianium and b&h based on high power pulsed laser sources and gated SPAD detector modules. The system in Milan aimed at high throughput single-optode acquisition, while the Berlin setup was equipped with a fully non-contact scanning stage for continuous measurements over a large area. Quite a high S/N ratio was achieved, as a result of the gating capability permitting to exploit the high laser power; as well as of the tight spatial confinement of the short distance measurements. Despite the extension of the scanned area, yet valuable time-traces could be extracted per each pixel, demonstrating high localization of the activation around the C3 point, resulting from the increase in spatial resolution in the short interfiber distance approach.

Partners involved: P1A PoliMi_FIS, P2 PTB, P4 IBIB PAN, P11 UniFi, P15 MPD

Task 1.2: Tomographic approaches

UCL_CS developed a tomographic reconstruction scheme exploiting apriori information derived from an MR based atlas. An anatomical atlas of the neonatal infant head was created, consisting of seven segmented MR images, coregistered to a common surface shape. The atlas can be deformed to correspond to the shape of the subject's head, using anatomical landmarks, surface points and optode positions. Results suggest that improvement can be achieved over using homogeneous background optical model. Both PoliMi_FIS and PTB explored reconstruction capabilities by exploiting time-encoded depth information. In particular, tests on simulations demonstrated the capability of depth-sectioning (time-resolved optical stratigraphy) by using the time-derivative of photon reflectance distributions.

UCL_MPB used computer simulations and phantom experiments to assess spatial resolution and contrast in diffuse optical tomography as a function of feature depth below the surface. The spatial resolution and location accuracy both exhibited a strong linear relationship with depth, whereas the contrast decreased exponentially with depth. Further, optimal selection of the Tikhonov regularization parameter on the accuracy of quantitation of optical properties was identified.

Partners involved: P1A PoliMi_FIS, P2 PTB, P3A UCL_MPB, P4 IBIB PAN, P3C UCL_CS

Task 1.3: Dense topographic approach

PoliMi_FIS implemented a system based on a single injection point and a gated ICCD for detection, collecting light re-emitted from a 6 cm diameter area while shielding points around the injection source. The system was tested applying the NEUROPT Protocol (see WP5) on inhomogeneous phantoms made of liquid solutions and black PVC cylinders.

IBIB developed a time-gated ICCD based workstation exploiting dense, large area light harvesting. Results on 3 volunteers showed that the system allows visualizing absorption changes during motor cortex stimulation. Yet, the proposed method does not allow for assessment of hemoglobin concentration because the system operates at a single wavelength. Critical problems are light coupling at the human head and the presence of hair. In the latter case, for subjects with short hair of constant length, the hair can be treated as a scattering filter, just limiting spatial resolution.

Further, IBIB demonstrated time-resolved near infrared light detection on the head surface at very large source-detector separation up to 9 cm, using a powerful laser source in combination with a sensitive photodetector positioned directly on the surface of the head. Measurements on a physical phantom demonstrated that a bolus of ICG can be detected down to a depth of 5 cm. Similarly, measurements on healthy volunteers suggested that the signals measured at an interfiber distance of 9 cm contain larger contribution from the brain than at shorter interoptode distances. At larger source-detector distance return of the signals to the initial level is faster than that noted at shorter distances, in line with the fact that in healthy subjects the dye does not undergo extravasation.

Partners involved: P1A PoliMi_FIS, P2 PTB, P4 IBIB PAN, P15 MPD, P16 bh

Task 1.4: Multi-spectral approach

UCL_MPB performed theoretical and numerical modeling investigations to identify optimal combinations of two, three, and four wavelengths for diffuse optical imaging. The purpose of this study was to inform the selection of wavelengths to be used in subsequent in vivo imaging studies using the supercontinuum laser. Three selection criteria were chosen: adequate separation between concentrations of oxy- and deoxy-haemoglobin, adequate separation between scatter and absorption, and maximal overlap of sampled volumes. Results suggested that the optimum combination choice of three wavelengths in this situation is 680±5 nm, 725±10 nm, and 876±12 nm, although the precise selection of wavelengths is not as critical as originally supposed.

IBIB developed two setups for multiwavelength acquisition, based either on the detection of ICG fluorescence by parallel acquisition over 16 spectral channels or on the measurement of diffusely reflected light using a supercontinuum source provided by Fianium over the absorption spectra of ICG. The systems were enrolled in phantom and in vivo measurement. The increase of the mean time of arrival of fluorescence photons detected at longer wavelengths may hint that these photons originate from the deeper layers of the medium. Further, the detection of the fluorescence signal at the longer wavelengths of the dye emission spectrum may permit eliminating the reabsorption effect which influences the time course of the signal. For what concern diffuse reflectance measurements, a large contribution of fluorescence photons remitted from the tissue was observed in time-resolved signals detected at longer wavelengths, thus indicating that the filtration of the fluorescence light may be essential in analysis of inflow and washout of ICG using time-resolved reflectometry

PoliMi_FIS studied the effect of the wide bandwidth of the laser source on the accuracy of the reconstructed chrormophores when using a supercontinuum source. In particular, the problem of spectral selection of the source was addressed. Two approaches were explored, namely the use of AOTF and of a rotating prism coupled with an adjustable slit. The former is optimal for speed of execution and flexibility, while the latter is superior both in terms of total light harvesting (no polarization losses) and of quality of the selected spectral bandwidth, with smaller side lobes.

PTB tested the feasibility of fast wavelength switching using a supercontinuum laser with AOTF by employing the 'FSK' mode, i.e. triggering by an external digital pulse train. The switching time was measured directly by recording the AOTF output in the triggered accumulation mode of a TCSPC board. It was found to be on the order of 3 ns. This is by far sufficient to realize the sequential multi-spectral acquisition, thus proving the feasibility of real time wavelength switching.

Partners involved: P1A PoliMi_FIS, P2 PTB, P3A UCL_MPB, P4 IBIB PAN, P13 CPPM, P14 Fianium, P16 bh

Task 1.5: Multi-modality imaging approach

The PTB time-domain Brain Imager prototype was coupled, in collaboration with Charité, with an EEG device, adding also recordings of a number of physiological signals like ECG, EMG, respiration, skin conductance, blood volume pulse, temperature. The presentation unit provided digital marker signals for synchronization. All individual devices are approved for clinical use.

UCL_MPB completed an extensive development and validation of probes for simultaneous diffuse optical imaging and EEG, complemented with functional stimulus tools and dedicated software for temporal registration of optical and EEG data. The multimodality imaging approach was tested on a range of phantoms designed specifically for simultaneous EEG and optical imaging. Appropriate protocols were designed for use in clinics. Finally, the integrated instrument was equipped with software for automated detection of seizure-related activity and movement-related artefacts.

PoliMi_FIS equipped both a dual channel fNIRS prototype and its clinical prototype with fNIRS-EEG coregistration capabilities, integrating a 19 channels EEG system that can provide also physiological data as breath frequency and heartbeat. A stage for stimuli presentation was also included. The entire apparatus was synchronized using a trigger signal provided by the fNIRS system and registered in one EEG channel so to align hemodynamic and electrical signals at data analysis.

PoliMi_BIO developed methodologies for integration of EEG-fNIRS and EEG-fMRI data. In order to integrate neurophysiological information with the haemodynamic responses coming from fMRI and fNIRS, different approaches of time-frequency analysis of the multichannel EEG have been implemented and used for the estimation of regressors related to the power variation of the relevant EEG rhythms and that were subsequently used in the design matrix for GLM analysis.

A major goal within WP1 was the assessment of the optical properties of the head. Key results were obtained adopting five different experimental set-ups, operated both in the time-domain and in CW at multiple wavelengths and different source-detector arrangements. The analysis was performed using analytical solutions of the Diffusion equation for a homogeneous, a two-layered, and a MRI-based structured medium. Around ten healthy volunteers were enrolled in the study. Six partners (ILM, PoliMi_FIS, UniFi, PTB, UCL_CS) took part in the experiment and data analysis. Results were compiled in a Database that is discussed in Deliverable D1.2 and uploaded on the public section of the NEUROPT site. As confirmed also by simulations, CW approaches provide information on the most superficial layers (scalp, and – only for absorption – the skull), while multi-layered time-resolved reconstructions can give

insight into the deeper structure (white matter, and clear layer). All methods display a similar range of variability, ascribed to the inter-subject differences.

Partners involved: P1A PoliMi_FIS, P2 PTB, P9 ILM, P3C UCL_CS, P11 UniFi, P1B PoliMi_BIO

Deliverables:

- D 1.1: Report on novel optical methodologies to improve the sensitivity, resolution and quantitation of diffuse optical imaging of the brain
- D 1.2: Database of optical properties of the head

WP2 Development and testing of novel photonic devices

Start month: 1
End Month: 33
WP Leader: P14 Fianium

Task 2.1: Development and testing of novel laser sources

Partner 14, Fianium have delivered to system integration partners PTB, UCL, PoliMi_Fis and IBIB PAN within the project, customised supercontinuum fibre lasers to investigate various diffuse optical imaging techniques and system architectures using this novel light source.

Furthermore, AOTF (Acousto-Optic Tuneable Filter) systems have also been provided to or acquired by partners PTB and UCL to investigate multi-spectral approaches to diffuse optical imaging. The AOTF systems have been customised to provide wider bandwidth coverage, higher power throughput and very fast rise-time modulation.

Supercontinuum sources have been evaluated by system integration partners and compared to existing pulsed laser diode illumination sources. Findings show that the supercontinuum provides significantly increased output power and greater flexibility in wavelength selectivity. However, the long-term power stability of the supercontinuum which is based on an inherently noisy process has proven to be somewhat problematic for instrumentation performance.

Between partners P14 Fianium and P13 CPPM, a novel light source based on four wave mixing (4WM) in photonic crystal fibres (PCF's) has been developed which provides high power concentrated in specific spectral ranges important to diffuse optical imaging of the brain.

Partner CPPM has designed and fabricated a large number of novel PCF's which produce 4WM signal pulses in the 700nm to 900nm spectral range when pumped by a 1064nm modelocked fibre laser.

Fianium have integrated two specific PCF's into a dual-output laser source, delivering high power pulses at 710nm and 820nm, each output having closed loop power control to enable excellent power stability. In excess of 2Watts has been delivered by each output but the system was limited to approximately 120mW per output at 40MHz, which is an order of magnitude higher than conventional diodes, with shorter pulse duration.

This system has been delivered to Partner P1A PoliMi_Fis for evaluations, which continued within WP4.

Partners involved: P13 CPPM, P14 Fianium, P1A PoliMi_FIS, P2 PTB, P3A UCL_MPB, P4 IBIB PAN

Task 2.2: Development and testing of novel detectors

Development of novel detectors - P15 (MPD) designed, developed, tested and delivered the module for single-photon detection with fast time-gating and sub-nanosecond transitions (fast-gated SPAD system). Such prototype includes the SPAD detector, the front-end electronics, the control electronics, the user interface, the optics and the micro-positioning mechanics. MPD, in collaboration with P1 PoliMi_FIS, has also designed and mounted on a micro positioning stage a custom focusing optics able to minimize losses in the coupling between the 1-mm core optical fibre and the SPAD active area. P15 MPD designed and provided also a home-made fast pulse generator, in order to properly gate-on and –off the SPAD detector with fast rising and falling edges. The trigger-in can be set either internally or externally, with a threshold selectable between 2.5 V and 2.5 V (5 mV resolution). The internal trigger ranges from 40 Hz to 133 MHz. The gate-on duration can be selected from 200 ps to 510 ns. A high-speed shaper speeds the transition times up to about 50 ps. Finally, an ultra-fast output driver amplifies the pulses and provides output pulses with amplitudes from 2.5 V to 8.5 V.

The optical response of the fast-gated SPAD was very flat and uniform, even with 200 ps rising edges, thus attaining very low time-jitter timing responses of about 60 ps, with diffusion tail of 240 ps or 90 ps for 200µm and 100 µm SPAD devices, respectively. The photon detection efficiency was 18% at 800 nm and the dark counting rate less than 50 kcps. The fast-gated system was deployed to partner P1 PoliMi_FIS, where it was integrated into photon migration apparatus and it was extensively tested and used in many measurement sessions.

P15 MPD also designed a fast-gated counter in order to employ SPAD detectors in counting mode, instead of the typical Time-Correlated Single Photon Timing mode, which requires expensive and bulky instrumentation. The counting window is generated starting from a reference 'sync' signal. A programmable delayer shifts in time the counting window with respect to the 'sync' signal with a resolution of 10 ps and a full scale range of 10 ns. A Gate generator guarantees rising and falling edges of tens of picoseconds for enabling the counting of SPAD ignitions. Finally, the counter sends the data to a PC through an USB 2.0 link. The minimum gate window is 65 ps FWHM wide and can be increased up to 10 ns with a resolution of 100 ps. MPD proved a maximum count rate greater than 100 MHz in burst mode (maximum continuous count rate of 16 Mcps due to the maximum value that can be stored into the CMOS counter).

The fast-gated counter was integrated into the photon migration apparatus together with the fast-gated SPAD and it was tested and used in measurement sessions together with P1 PoliMi_FIS. P15 MP proved the possibility to reconstruct the instrument response function and the time-resolved reflectance curve by using a diffusive phantom on a wide dynamic range.

Eventually P15 MPD pushed forward the development of arrays of CMOS SPADs, like a linear array (32 SPADs on a row) that can be operated both in photon counting and in photon timing, and also in gated mode with rise-times of about 700 ps, with timing jitter of each pixel less than 100 ps, dark count rate of about 4 kcps and detection efficiency of 7% at 800 nm.

Testing of novel detectors - P15 MPD and P1 PoliMi_FIS collaborated to conceive and develop an experimental setup for photon migration measurements based on the fast-gated SPAD. A supercontinuum fibre laser (provided by P14 Fianium) delivers white-light picosecond pulses at 40 MHz repetition rate. An Acousto-Optic Tuneable Filter selects a wavelength between 600 nm and 1000 nm, with a spectral resolution of about 5 nm.

We proved that the workstation for photon migration measurement based on fast-gated SPAD has a very wide dynamic range (larger than 7 decades) even at very short time delays, few nanoseconds, and up to tens of ns, corresponding to investigate regions of various cm under the tissue under investigation.

P15 MPD and P1 PoliMi-FIS also performed preliminary measurements to prove the advantages of the fast-gated counter approach to photon migration measurements. A counting window of 100 ps width was shifted at steps of 100 ps in order to sample the curve at different delays. Results proved the possibility to obtain a wide dynamic range by counting photons in the desired sharp counting windows at a high count-rate, exploiting the larger power made available by the novel laser sources.

Partners involved: P15 MPD, P1A PoliMi_FIS, P2 PTB, P16 bh.

Task 2.3: Development and testing of novel electronics

The general development target was to provide time-resolved detection electronics with a timing stability on the order of a few ps and a large number of recording channels. The recording speed should be fast enough to record physiological changes of the oxygen saturation in the human brain. Several approaches were followed up:

1. *Devices based on the TAC/ADC principle*: Multichannel TCSPC devices were provided by operating up to eight TCSPC boards in a PCI extension box connected to a PC or a laptop computer. The electrical time resolution is 3 ps rms, the minimum time channel width 820 fs. The timing drift is on the order of a few ps over 15 minutes. The devices can be operated with fast source and wavelength multiplexing. The number of modules is limited by the power consumption. Attempts to reduce the power consumption without sacrificing timing stability and resolution were found not promising.
2. *Devices based on TDC chips:* Multichannel TCSPC devices with 6 parallel channels on a single board were developed. The boards are using two 8-channel TDC chips from ACAM GmbH, Germany. To obtain a reasonable differential nonlinearity with these chips a differential dithering technique was developed and implemented. Test measurements with phantoms showed that the devices are able to measure correct optical properties. A second development based on a new ACAM chip was not successful. Although the intrinsic time resolution and differential nonlinearity was better than for the 8-channel chip the timing stability was insufficient for DOT. The reason was chip-internal interaction of the recording with the TDC core voltage, which causes a count-rate dependent timing spread.
3. *Data Compression:* Data compression was implemented in a new TSCPC module. The module uses the TAC-ADC principle. However, instead of building up photon distributions, it directly determines the photon number and the first and second moment of the photon distribution, and transfers these values into the computer.
4. *Sequential recording and multiplexing capabilities:* The TAC-ADC designs were upgraded with extended multiplexing capabilities. In combination with the Fianium lasers, eight wavelength channels can be multiplexed at microsecond speed. Wavelength multiplexing can be combined with spatial multiplexing via fibre switches or galvanometer scanners. The result is quasi-simultaneous recording in a large number of wavelength and position channels at a speed fast enough to record physiological changes in the brain.
5. *Hybrid detectors:* A hybrid detector module was developed within the project as an unplanned activity. Time-of-flight distributions obtained with this detector are free of after pulsing background and free of bumps or tails. For a given number of photons, optical properties are obtained at higher accuracy than with previously used detectors.

Partners involved: P16 bh, P15 MPD, P1A PoliMi_FIS, P2 PTB, P3A UCL_MPB, P4 IBIB PAN.

Deliverables:

- D 2.1: Tailored state-of-the-art photonic devices (laser sources, photo detectors, TCSPC electronics)
- D 2.2: Novel photonic devices (laser sources, photo detectors, TCSPC electronics)

WP3 – Modelling and Computation

Start month: 1
End month 36
Work package leader: P9 ILM

Task 3.1: Forward Problem

UniFi has developed a flexible software package that can be used as forward solver for photon migration through biological tissue. Photon migration can be simulated in several homogeneous and inhomogeneous geometries. The package, which is made available for the public, consists of several solvers based on solutions of the diffusion equation (DE) and on Monte Carlo (MC) codes. In details UniFi developed:

- FORTRAN subroutines providing solutions of the DE through two and three-layer slabs
- A MC code for photon migration through a layered medium for a number of layers up to four (with and without inhomogeneities inside)
- A software package of several subroutines providing solutions of the DE and hybrid models based on radiative transfer equation and DE. These solutions are applicable for the infinite medium, the slab (homogeneous and two-layered), the parallelepiped, and the cylinder. The perturbed solutions are also available. The source codes have been written using the FORTRAN language and the subroutines can be composed like a mosaic to perform various calculations of the physical quantities used in photon migration.
- The Diffusion&Perturbation software dedicated to the calculation and to the visualization of the solutions of the DE and of its perturbation theory for a homogeneous medium. This software package has a user-friendly interface. With this software the calculations of typical data types as the steady-state and the time-resolved reflectance, transmittance and fluence rate, are implemented.
- A set of Monte Carlo results has been also provided that can be used for validating the analytical models provided with the above mentioned software packages
- A FORTRAN subroutine that calculates a high order perturbation theory for the time domain for describing absorption perturbations based on the moments of the generalized temporal point-spread function. The method of Padé approximants is used to extend the validity of the theory to a wider range of absorption contrasts between defects and background. This forward solver can be used to calculate the effect of black defects.
- A forward solver for time and steady-state domains based on the Born approximation for simulating the effect of small-localized fluorophores embedded inside a non-fluorescent biological tissue. Some subroutines written in FORTRAN that can be used for calculating the fluorescent signal for the infinite medium and for the slab have been provided.

UCL_CS has implemented a time-domain finite element method (TD-FEM) forward solver of DE for light transport in inhomogeneous media with complex boundaries within the framework of the TOAST software package, and published for general download. An estimation of the temporal intensity profile from moments of the temporal distribution has been added to improve performance of time-domain forward solver. In addition, the software has been extended to support discontinuous Galerkin FEM to account for parameter discontinuities at internal boundaries, and the boundary element method (BEM) to improve the simulation of piecewise constant problems. UCL_CS has also added support for graphics

processing unit (GPU)-based computing to the TOAST package, providing significant performance improvements. Several important achievements and deliverables have been:

- TOAST software package made available to all partners
- Time domain data types and estimation of temporal profile from moments implemented in TOAST
- Discontinuous Galerkin FEM including refractive index-mismatched internal boundaries, and BEM forward solvers implemented in TOAST
- Performance optimisation of forward solver with GPU acceleration

ILM has derived analytical solutions of the diffusion equation for a variety of geometries in the steady-state, frequency, and time domains. Solutions for an arbitrary number of layers were derived for the

- semi-infinite geometry
- cylinder (both axially and radially layered)
- concentric sphere
- rectangular parallel-epiped

In addition, solutions of the simplified spherical harmonics equations were obtained for the infinitely extended medium and for the semi-infinite medium for all domains. Further, solutions of the radiative transfer equation were derived for the infinitely extended scattering medium both for the fluence and the radiance again for all domains. Finally, solutions were found for the semi-infinite medium considering the exact boundary conditions using Fresnel's equations. The solutions were compared to Monte Carlo simulations and within the statistics of the simulations an exact agreement was found. All the solutions were derived for different incident sources. A variety of analytical solutions for the diffusion equation and for the radiative transfer equation were made available for public download. PoliMi_FIS, PTB, UCL_MP, and IBBE provided experimental data for validation of the forward models.

Partners involved: 1 (PoliMi_FIS), 2 (PTB), 3 (UCL_MP), 4 (IBBE), 9 (ILM), 10 (UCL_CS), 11 (UniFi)

Task 3.2 Inverse Problem – General

UCL_CS has explored Markov-chain Monte Carlo (MCMC) reconstruction of piece-wise homogeneous optical parameters in pre-defined regions. This can be used as a first step in a two-step reconstruction, followed by voxel-based reconstruction. Jacobian-free inverse solver method has been implemented in the TOAST software package to eliminate memory requirements for matrix storage.

The GPU acceleration of TOAST forward calculation increases efficiency of the inverse computation. UCL_CS have incorporated use of CUSP sparse linear solver package in the TOAST package which provides GPU acceleration for iterative Krylov solvers. Some of the main results are:

- MCMC reconstruction of piecewise constant region parameters
- Jacobian-free implementation of inverse problem in TOAST
- GPU-acceleration of inverse problem in TOAST

PoliMi_FIS, PTB, UCL_MP, and IBBE provided experimental data for validation of the inverse models.

Partners involved: 1 (PoliMi_FIS), 2 (PTB), 3 (UCL_MP), 4 (IBBE), 10 (UCL_CS)

Task 3.3 Inverse Problem – Optical Properties as Priors

UniFi has developed a FORTRAN subroutine for inversion procedures based on an Optimal Estimation (OE) algorithm. The OE can account of a-priori information both on target and forward model parameters. When a-priori information is not available the OE is not different from other Non-linear Least-Square Fit (NLSF) routines, such as those based on the Levenberg-Marquardt algorithm. This is particularly true for an over-determined set of data from which the target parameters can be indifferently reconstructed using the OE or other NLSF routines. On the contrary, when we are dealing with an under-determined set of observations to retrieve a certain set of target parameters, the availability of a-priori information on the target parameters or on the forward model parameters can significantly improve the quality and the stability of the retrieval. The improvement in the retrieval obtained with the OE can be summarized as follows:

- A-priori information on target parameters on average determines a lesser difference between retrieved values and true values of the target parameters, thus showing a greater accuracy in the procedure
- A-priori information on target parameters determines lower error bars on the retrieved parameters, thus testifying to a greater stability and precision in the procedure
- A correct estimation of the errors on the forward model parameters improves the accuracy of the retrieved target parameters

It was found out that the computation time of the OE routine is roughly a factor two slower compared to the Levenberg-Marquardt algorithm.

ILM has programmed and investigated an artificial neural network (ANN) to solve the inverse problem. The forward problem was solved using solutions of the layered diffusion equation that simulated time-resolved reflectance curves in a five layered model of the human head. After the training process the ANN determined the absorption coefficient of the brain (fifth layer of the model). Further, the optical properties of scalp and skull (first and second layer of a forth layered model) were determined after the ANN was trained with simulated spatially resolved reflectance curves (SRRC) using Monte Carlo simulations (MCS). In addition, the ANN determined the optical properties from liquid phantom measurements after it was trained with MCS simulating SRRC.

The derived analytical solutions of the diffusion equation were used to reconstruct successfully the optical properties for layered scattering tissue in the time domain considering especially the two layer case. In the steady-state domain solutions of the diffusion equation and Monte Carlo simulations using e.g. scaling principles were applied to reconstruct the optical properties of scattering media. For the reconstruction of the optical properties with the diffusion theory the codes were made available for the partners.

PoliMi_FIS, PTB, UCL_MP, and IBBE provided experimental data for validation of the inverse models.

Partners involved: 1 (PoliMi_FIS), 2 (PTB), 3 (UCL_MP), 4 (IBBE), 9 (ILM), 11 (UniFi)

Task 3.4 Inverse Problem – Anatomical and Spectral Priors

UCL_CS has added support for spatially varying and edge-preserving application of regularisation during the reconstruction of 3D volume images to the TOAST software package. This allows the use of a-priori known edge information, which can be derived from complementary imaging modalities (X-ray CT, MRI) used on the subject, or from probabilistic region distributions from atlas data.

UCL_CS has also developed use of anatomical atlas of the infant head to guide reconstruction. Markov-chain Monte Carlo and anatomical prior information were used to reconstruct optical parameters of the human head from time-domain optical measurements. Direct reconstruction of chromophore

concentrations and scattering parameters from multispectral measurements were also implemented. Some significant results are listed below:

- Characterization of improvement achieved using anatomical atlas data in brain activation imaging; simulated case
- Multispectral approach for direct reconstruction of spatial distribution of chromophore concentrations has been implemented in the TOAST software package
- Support for use of prior edge information implemented in TOAST
- Optical parameters of the head reconstructed from time-domain optical data using individual anatomical information

PoliMi_FIS, PTB, UCL_MP, and IBBE provided experimental data for validation of the inverse models.

Partners involved: 1 (PoliMi_FIS), 2 (PTB), 3 (UCL_MP), 4 (IBBE), 10 (UCL_CS)

Deliverables:

- D 3.1: Binary release of software for refined and validated forward models
- D 3.2: Binary release of software for refined and validated inverse models
- D 3.3: Report on optimisation of forward and inverse models for use in clinics

WP 4 Development of instrumentation for clinical applications

Start month: 1
End Month: 39
WP Leader: P3A UCL_MPB

Task 4.1: Adapting prototype time-domain instruments for specific clinical applications

The aim of this task was to ensure that four imaging systems were available for clinical evaluation by the end of month 12 of the project.

P2 PTB's prototype was technically ready at the onset, but required modifications to accommodate
- diffuse and fluorescence imaging of ICG boli in the brain, and
- combined optical and EEG recording during functional activation studies.

Two new picosecond laser diodes (both at 780 nm) and a fast motorised filter holder were incorporated into the system to facilitate the ICG measurements for a successful programme of studies on stroke patients in collaboration with partners P6 Charité and P4 IBIB_PAN. Three different diode laser sources (690 nm, 800 nm, and 830 nm) were incorporated into the system for the function activation studies, in order to quantify changes in concentrations of oxy- and deoxy-haemoglobin. In collaboration with P6 Charité, the P2 PTB optical imager was combined with a clinical multi-channel EEG system, and then evaluated on volunteers using motor and visual stimulation paradigms. Modifications to the P2 PTB system were carefully designed to facilitate a switch between the two configurations within two hours.

The P4 IBIB_PAN system, constructed before the project began, was modified to improve light detection efficiency and reduce complexity by reducing the number of active sources and detectors. The prototype system was also adapted to enable very rapid switching between a (ICG) fluorescence detection mode and a diffuse reflection detection mode. This involved incorporating rotating filters into the system optics.

Measuring fluorescence involves using a longpass filter which blocks the 760 nm excitation light, while measuring reflectance uses a shortpass filter to block the fluorescent light.

A previous imager built by P1A PoliMi_FIS was upgraded to produce a new compact modular imaging system, incorporating new thermoelectrically-cooled PMT detectors (with greater sensitivity), fibre bundles (with increased flexibility and transparency), and read-out electronics.

The first generation P3A UCL_MPB time-resolved imaging system had been successfully employed in the clinic well before the start of the project and did not require further updates. Therefore P3A UCL_MPB focussed its effort on building a completely new imager (task 4.3) with superior performance in consultation with P16 bh and P14 Fianium.

Partners involved: P1A PoliMi_FIS, P2 PTB, P3A UCL_MPB, P4 IBIB PAN, P13 CPPM, P14 Fianium, P16 bh

Task 4.2: Development of fibre-holding probes/helmets for clinical applications

A broad variety of fibre-holding probes were developed by project partners for a range of different brain-imaging applications, with particular emphasis on probes suitable for simultaneous optical and electroencephalography (EEG) measurements. P2 PTB combined a commercial EEG 'Easy Cap' (containing ring electrodes) with optical fibre bundles to facilitate functional stimulation and long-term sleep studies. To maintain a constant 3 cm separation between optodes, flexible plastic strips were added to the underside of the elastic cap. Meanwhile P4 IBIB_PAN modified a conventional EEG cap, with optical sources placed at the C3 and C4 positions (according to the 10:20 system), and four detectors located at a fixed distance of 3 cm from each source. Holes in the ring electrodes were enlarged to enable collocation of the electrodes and optical fibres. Likewise P1A PoliMi_FIS based their probe on an EEG cap, modified to support multiple source and detector fibres. Their design enabled underlying hair to be moved away from the fibres mechanically or using gentle air pressure. The final version incorporated spring-loaded fibre holders, which ensure good contact is maintained between the fibres and the scalp throughout head movement, and a fibre mounting system which ensures the fibres connect at right-angles to the surface and supports the weight of the fibres. P3A UCL_MPB constructed optical/EEG probes for studies of infant seizures. These were based on custom-made 'opto-electrodes' which consist of standard Ag-AgCl cup electrodes which are modified to support an optical fibre behind an optical window in the centre of the cup. Optically-transparent, electrically-conducting gel is used to couple each opto-electrode to the scalp. Two-part array probes were developed to support up to eleven opto-electrodes on each hemisphere of the infant head.

P2 PTB developed another head probe for measurements of activity during cognitive tasks. This coupled one optical source and two detectors to each hemisphere using a neoprene fibre holder secured using Velcro straps.

P3A UCL_MPB made major modifications to an adjustable helmet to be used for 3D optical imaging of the entire infant brain, to accommodate a greater range of head shapes and sizes. The helmet can support up to 32 optodes (combined sources and detectors) and consists of three distinct sections: a flexible base pad, which supports the weight of the head; a flexible top pad, which covers the frontal region of the head; and a fixed coronal section which contains radially-translatable optodes which cover the top and sides of the head. Soft black foam rings surround the end of each optode on the inner surface of the helmet. These are replaced after each infant scan to prevent cross-infection between infants.

Partners involved: P1A PoliMi_FIS, P2 PTB, P3A UCL_MPB, P4 IBIB PAN

Task 4.3: Development of new instrumentation

This task required P1A PoliMi_FIS, P2 PTB, and P3A UCL_MPB to develop a new generation of optical imaging systems, using state-of-the-art components.

P15 MPD designed and built two new compact modules based on fast-gated SPADs. The two modules fit within a 19-inch rack with all the optical and electronic components needed to operate a SPAD in fast time-gated mode. The 100 nm active-area silicon SPAD exhibited a remarkable timing resolution of about 50 ps, and the durations of the rising/falling edges are about 200 ps. Illumination with continuous uncorrelated light exhibited a very uniform flat response, thus establishing the linearity of the response of the system. The P15 MPD time-gated modules were incorporated into a second-generation time-resolved functional system developed by P1A PoliMi_FIS, which also employs a four-wave mixing (4WM) laser provided by P14 Fianium. The 4WM laser delivers two trains of short (50 ps) pulses at a repetition rate of 40 MHz at two wavelengths (710 nm and 820 nm), with an average power of up to 95 mW at each wavelength. Power is equalised at the two wavelengths using two stacks of variable attenuators, providing an attenuation of up to 160 dB. A 2x2 optical switch enables each detection channel to acquire a measurement from two source channels, one wavelength at a time.

A second-generation system developed by P2 PTB employs new cooled PMT modules with greater quantum yield and red sensitivity than PMTs used previously. Each of four PMTs were incorporated into a separate custom-made detector module which feature new relay optics, a motor-controlled variable optical attenuator, and a filter wheel accommodating up to 5 filters. To accommodate an increased number of measurement positions, a new optical setup using diode laser modules (at 705 nm and 830 nm) was implemented. To increase the number of effective sources, the laser output is multiplexed to five source positions per hemisphere. The pulse trains are interlaced using source fibres of different lengths. The system switches rapidly between the two source wavelengths. Partner P16 bh provided P2 PTB with a SPC-160 prototype TCSPC unit which performs calculations of the moments of time-of-flight histograms, thus significantly reducing the amount of data needed to be transferred to, and stored by, the PC.

P3A UCL_MPB developed a second-generation time-domain imaging instrument for performing optical tomography studies on newborn infants in the clinic. The system employs 32 thermoelectrically cooled PMTs, each coupled to a detector fibre bundle via a computer-controlled custom-built variable optical attenuator (providing attenuation of up to 37 dB). The PMTs are coupled to the four independent timing engines on a P16 bh TCSPC unit via four 1x8 routers. A pulsed supercontinuum laser and customized dual-AOTF unit provided by P14 Fianium have been fully integrated into the system, enabling data to be collected at any four wavelengths (over the range 600 nm – 1100 nm) simultaneously. The laser output is coupled to one of 32 source fibers (each integrated along the central axis of one of 32 detector fibre bundles) via a computer-controlled 32-way switch. Thus the device can collect up to 32 x 32 histograms of photon flight times at four different wavelengths. The temporal resolution of the system (the FWHM of the impulse response) is around 220 ps.

Partners involved: P1A PoliMi_FIS, P2 PTB, P3A UCL_MPB, P4 IBIB PAN, P13 CPPM, P14 Fianium, P15 MPD, P16 bh

Deliverables:

- D 4.1: First generation laboratory prototypes ready for use in a clinical environment
- D 4.2: Specific probe/helmet designed and optimised for clinical tests
- D 4.3: Second generation laboratory prototypes ready for use in a clinical environment

WP5 Standardisation and quality assurance

Start month: 1
End Month: 48
WP Leader: P2 PTB

Task 5.1: Definition of standardized protocols for characterization of instrumental parameters, assessment of uncertainty of relevant measurands, and routine tests for quality assurance during clinical applications

Definition of standardized protocols: As a result of collaborative work of all partners involved, Deliverable 5.1 defined common procedures to assess and compare the performance of research instruments for time-domain optical imaging of the brain, i.e. their capability to measure optical parameters of the human brain that are relevant for clinical applications.

Three individual protocols have been included:
- 'Basic instrumental performance',
- Performance assessment by measurements on homogeneous phantoms ('MEDPHOT protocol')#
- Performance assessment by measurements on inhomogeneous phantoms ('NEUROPT protocol'), the first two of which were developed within the project.

The protocol 'Basic instrumental performance' is devoted to the characterization of time-domain instruments in a direct way, without any sample (phantom) and with minimum involvement of data analysis.

This protocol consists of the following tests:
- Source parameters
- Responsivity of the detection system (a completely new test to characterize the efficiency of the detection part of instruments)
- Temporal instrument response function (IRF) and its stability
- Differential nonlinearity

The 'NEUROPT protocol' is related to Performance assessment by measurements on inhomogeneous phantoms. It addresses the major goal of time-domain optical brain imaging to detect, localize and quantify changes in the optical properties (in particular of the absorption coefficient) of the brain and to eliminate the influence of extracerebral tissue on the measurement. Its tests are related to Sensitivity (Contrast; Contrast-to-noise ratio), Spatial resolution (Depth selectivity; Lateral spatial resolution) and Quantification of absorption changes (Accuracy; Linearity).

Definition of pre-norms for standardization and quality assurance: Deliverable 5.4 contains improvements of the standardized protocols, taking into account the practical experience from the performance comparison of instruments (Deliverable 5.3). It includes the specifications of the implementation (phantoms, measurement conditions) of the tests as well as a consolidated reporting sheet. The various tests can be adopted in a possible future development of standards for clinical devices based on this technology. Based on their experience gained in this WP, PTB and PoliMi_FIS contribute to beginning international standardization activities related to (cw) fNIRS.

Partners involved: P1A PoliMi_FIS, P2 PTB, P3A UCL_MPB, P4 IBIB PAN, P9 ILM, P3C UCL_CS, P11 UniFi

Task 5.2: Provision of suitable phantoms with known optical properties to perform the protocols defined in task 5.1

Liquid phantoms: The implementation of all tests of the 'Standardized protocols' relies on liquid (homogeneous and inhomogeneous) phantoms based on Intralipid as scattering medium and Indian ink as absorber. Both components were thoroughly characterized, i.e. scattering and absorption properties were determined with high accuracy (UniFi, PoliMi, ILM), the linearity of Intralipid dilutions was studied (ILM, UniFi) as well as the stability of optical properties and the reproducibility for different batches of Intralipid and brands of ink (UniFi). Carbon nanohorns were investigated as alternative absorber for tissue phantoms (UniFi).

To implement the NEUROPT protocol, small black PVC cylinders were used to mimic the perturbation due to small localized variations of the absorption coefficient. This was underpinned by theoretical studies (UniFi, PoliMi_FIS) on the equivalence between a perturbation by a small black inclusion and a finite absorption change in a larger volume.

UniFi provided the other partners with:

- well characterized samples of Intralipid and the Indian ink, together with instructions for preparing the dilutions to obtain desired optical properties;
- black scattering cells with small plexiglass windows for measurements in homogeneous and layered geometry;
- small PVC cylinders of various size

A multilaboratory study (9 laboratories) on accurate characterization of Intralipid and ink (5 NEUROPT partners and 4 laboratories from Canada (2), Spain and Sweden) for liquid phantoms has been led by PoliMi_FIS. A statistical analysis of the results has been performed by PTB. Wide consistency was found among results of different laboratories in spite of different techniques, instrumental set-ups and data analysis methods. Reference values were determined with a relative uncertainty of about 2% for Intralipid and 3% for ink.

Solid homogeneous phantoms for assessment of responsivity: Dedicated thick slab phantoms were developed, manufactured and accurately characterized (PTB), as working standards to provide nearly uniform scattering light sources with known radiance. These phantoms were distributed to the partners to perform the responsivity tests of the detection system of instruments.

Various other phantoms have been developed for specific test, e.g. solid homogeneous phantoms (PoliMi_FIS), layered solid phantoms (ILM), a complex solid multi-region slab phantom (UCL_MPB), electrically-activated dynamic solid phantoms with thermochromic targets (UCL_MPB).

Partners involved: P1A PoliMi_FIS, P2 PTB, P3A UCL_MPB, P9 ILM, P11 UniFi

Task 5.3: Characterization and performance assessment of various upgraded and novel instruments and their specific operating modes according to the protocol defined in task 5.1

Characterization and performance assessment was carried out for 8 instruments or instrumental configurations of 4 NEUROPT partners according to the Standardized Protocols (Deliverable 5.1) and based on the phantoms developed in task 5.2 (Deliverable 5.2). Apart from the clinical instruments, several laboratory instruments were included that were optimized for high time resolution or high detection efficiency. The following paragraphs give a short overview for the three individual protocols. The results were reported in detail in Deliverable 5.3.

Basic instrumental performance (BIP protocol) - Key results:

- The responsivity of the detection system, i.e. the overall efficiency to collect and detect light emerging from tissue, is obtained as the ratio of photon count rate and the amount of light from the tissue that enters the detector optode. The results of the responsivity measurements on the various instruments have been quantitatively compared. To our knowledge, this is the first quantitative comparison of this kind of different instruments (significant result).
- The substantially differing IRFs of various instruments were used in simulations to determine the influence of features of the IRF (afterpeaks) on contrast and noise.

MEDPHOT protocol: This protocol was performed on liquid homogeneous phantoms with a set of optical properties, in reflectance geometry. Based on the values retrieved for transport scattering and absorption coefficients, accuracy and linearity, noise as well as stability and reproducibility were assessed.

NEUROPT protocol: The measurements according to the NEUROPT protocol were performed in reflectance geometry, at a source-detector separation of 3 cm, with background optical properties $\mu s' = 10$ cm-1, $\mu a = 0.1$ cm-1. The assessment of contrast, accuracy and linearity was implemented by two different methods:

- using small black PVC cylinders immersed in a turbid solution at various z (depth) positions halfway between source and detector,
- using a two-layered medium with a Mylar foil at 10 mm depth separating both compartments. Starting from the homogeneous values, changes in the absorption coefficient were applied in each layer separately. The layered geometry also provides the assessment of depth selectivity which allows for a comparison across different instruments as well as quantities analysed. Lateral spatial resolution was assessed by x and y scans of a black cylinder at a depth of 10 mm. Two types of semi-empirical analysis were applied in the performance assessment of instruments, i.e. analysis based on (i) moments of distribution of times of flight and (ii) time windows.

Partners involved: P1A PoliMi_FIS, P2 PTB, P3A UCL_MPB, P4 IBIB PAN, P11 UniFi

Task 5.4: Characterization and performance assessment of various algorithms to reconstruct tissue parameters based on homogeneous and various inhomogeneous forward models

Provision of simulated data: UniFi has developed and used Monte Carlo codes to simulate photon migration both for homogeneous and non-homogeneous media that are available to generate reference results to check the performance of different algorithms.

Semi-empirical algorithms to detect absorption changes in the brain on simulated and in-vivo data: PTB in collaboration with PoliMi assessed the robustness of algorithms based on moments of distribution of times of flight (DTOF) and time windows of DTOFs, in particular regarding the influence of the shape of measured IRF on contrast and noise. Comparative tests of these algorithms applied for the analysis of motor stimulation experiments carried out by PTB, IBIB_PAN and PoliMi_FIS in 41 healthy volunteers (Tasks 7.2. and 6.1) were performed by IBIB PAN.

Advanced methods of retrieval of optical properties: The Optimal Estimation algorithm developed by UniFi as a software package to reconstruct the optical properties of homogeneous and two-layered media was successfully applied to experimental data obtained together with PoliMi_FIS on a two-layered liquid phantom.

Algorithms to determine absorption spectra in homogeneous turbid media: A comparison study on epoxy resin phantoms, between the spatially resolved reflectance (ILM) and the time resolved reflectance (PoliMi_FIS) has been performed and showed good agreement between both methods.

Image reconstruction algorithms: UCL_CS have applied the robust and efficient reconstruction techniques developed in WP3 to the tomographic reconstruction from simulated test data of time-resolved light transmission. For example, the approximation error method was tested.

Partners involved: P1A PoliMi_FIS, P2 PTB, P3A UCL_MPB, P4 IBIB PAN, P3C UCL_CS, P11 UniFi

Deliverables:

- D 5.1: Standardized protocols
- D 5.2: Calibrated tissue phantoms
- D 5.3: Report on characterization of instruments and algorithms for data analysis
- D 5.4: Definition of pre-norms for standardisation and quality assurance

WP 6 Processing and analysis of clinical data

Start month: 1
End Month: 48
WP Leader: P4 IBIB PAN

Task 6.1: Analysis of in vivo measurements

A software package for analysis of the time-resolved measurements on the head was developed. The procedures allow for analysis of distributions of times of flight of photons obtained from the head during brain oxygenation measurements using time resolved near-infrared spectroscopy (trNIRS). The toolbox was developed in the Matlab environment and consists of procedures for preprocessing of measured data, analysis of optical properties of the medium and calculation of oxy- and deoxyhemoglobin concentrations. A detailed description of the software package was provided in Deliverable 6.1.

An analysis of time-resolved signals acquired during the motor stimulation experimental campaign was carried out by all groups involved in these experimental studies. These analyses enabled the software to be optimized and its usefulness validated for planned clinical studies. P1A PoliMi_FIS, P4 IBIB and P2 PTB performed an analysis of motor stimulation in-vivo experiments carried out according to the common protocol. Partners implemented general principles of signal processing defined within the NEUROPT consortium. However, different algorithms for data processing were used by the partners to estimate changes in absorption coefficient as a function of depth in the tissue. Algorithms based on moments of the measured distributions of times of flight of photons and on the fitting of the diffusion equation solution were applied. Results of these analyses were reported in detail in Deliverable 6.2.

Data analysis was carried out for the signals acquired from patients suffering from acute stroke, epilepsy, and traumatic brain injury. These analyses were accomplished in cooperation between technical groups and their clinical partners (e.g. P1A PoliMi_FIS, P1B Polimi_BIO, P5 INNCB, P2 PTB, P6 Charité, P4 IBIB, P8 MUW, P3C UCL_CS). Results of these analyses enabled interpretation of the acquired data to be improved, and conclusions to be drawn about the feasibility of the trNIRS technique in clinical applications. The methodology of the data analysis was reported in detail within Deliverable 6.3.

The second-generation optical tomography system developed by UCL_MPB has been evaluated on newborn infants in the neonatal intensive care unit (UCL_IWH). Data is processed to extract temporal

moments at four wavelengths simultaneously. The response of the normal and pathological newborn brain to a passive motor stimulus was studied, and three-dimensional images were generated, representing the regional changes in blood volume. Full-brain images of premature infants with a variety of pathological conditions have also been acquired.

Partners involved: P1A PoliMi_FIS, P2 PTB, P3A UCL_MPB, P4 IBIB PAN, P5 INNCB, P6 Charité, P3B UCL_IWH, P8 MUW, P3C UCL_CS, P1B PoliMi_BIO

Task 6.2: Correlation with physiological data and other modalities

P1B PoliMi_BIO, P1A PoliMi_FIS, and P5 INNCB showed that an 'EEG informed' Generalized Linear Model (GLM) provides a novel tool for integrating EEG and NIRS data acquired from patients. This method had never been attempted before in the NIRS imaging field. P1A PoliMi_FIS in collaboration with P5 INNCB acquired a variety of physiological data (EEG, ECG, EMG, breathing, eye movement) during time domain fNIRS measurements on volunteers and patients using visual and motor stimuli. P1B Polimi-BIO analyzed data from healthy subjects and patients with neurological disorders by means of the GLM technique. After applying standard GLM analysis, in which the regressors are obtained from the time course of the task and from a priori assumptions on the noise characteristics, the GLM was modified in order to include information related to EEG and EMG.

P6 Charité and P2 PTB carried an analysis of long-term measurements which provide a unique view into the coupling behaviour of electrophysiological band activity (slow wave activity, delta and alpha activity) and the hemodynamic signal in relation to the sleep states. EEG/NIRS signatures were separately analysed for the different sleep states. Based on the sleep scoring of each subject, NIRS data were analyzed by means of a windowing procedure. Additionally, single trial analysis with subsequent correlation of EEG and NIRS signatures were performed for the non-REM sleep stage S3.

P3C UCL-CS has worked together with P2 PTB on combined MRI and optical measurements to reconstruct optical parameters of the scalp, skull, and brain from in-vivo measurements. The Markov-chain Monte Carlo was applied to provide an estimate of the shape of the minimum of the objective function used in the reconstruction. An approximation error method was applied to correct for the fact that the diffusion-based forward model used in the simulation does not take into account the low-scattering cerebrospinal fluid, and to compensate for inaccuracies of a 3-layer anatomical model.

UCL_MPB have correlated optical data with EEG measurements on infants diagnosed with seizures. Since all infants were treated with anticonvulsants, the EEG data were normal except for a slight depression in some cases. When available, UCL_MPB and UCL_IWH have employed MRI and cranial ultrasound data to assess correspondence between observed optical features and known lesions, such as haemorrhage.

Partners involved: P1A PoliMi_FIS, P2 PTB, P3A UCL_MPB, P4 IBIB PAN, P1B PoliMi_BIO

Task 6.3: Statistical methods

Time courses of oxy- and deoxy-genated haemoglobin changes were extracted by P1A PoliMi_FIS from time-domain fNIRS data acquired during measurements on volunteers and patients. P1B Polimi_BIO applied a GLM approach for data analysis. Specific design matrices were created, containing regressors modelling:

1) the baseline and rest periods of the tests,
2) the activation blocks of the tests, and

3) pre-processed electroencephalographic and electromyographic data.

Contrast arrays were designed to investigate:

1) the relationship between the activation induced by the protocol and rest,
2) the relationship between the activation blocks and the rest periods, and
3) electroencephalographic, electromyographic and electrocardiographic correlates, related to the functional activation induced by the task.

P4 IBIB and P8 MUW carried out a statistical analysis of the time shifts of bolus arrival to tissues in healthy volunteers and groups of patients. The statistical significance of differences between amplitudes of signals of moments was also analysed during inflow of the dye obtained in groups of subjects. The results of the statistical analysis showed that the most useful parameter for differentiation of the groups of patients studied is the delay between the bolus appearance obtained from the variance signal and the number of diffusely reflected photons.

Partners involved: P1A PoliMi_FIS, P2 PTB, P3A UCL_MPB, P4 IBIB PAN, P5 INNCB, P6 Charité, P3B UCL_IWH, P8 MUW, P1B PoliMi_BIO

Deliverables:

- D 6.1: Software for clinical data analysis available for all partners
- D 6.2: Complete analysis of the data acquired during the first measurement campaign
- D 6.3: Complete analysis of the data acquired during the second measurement campaign

WP7 Clinical Tests

Start month: 1
End Month: 48
WP Leader: P6 Charité

Task 7.1: Definition of protocols & ethical

Partners of work package 7 obtained the ethical approval from their institutions in order to perform the measurements in healthy subjects and patients by means of time-domain NIRS (tdNIRS).

IBIB_PAN received the ethical approval to study oxygenation and perfusion in patients with brain haemorrhage. Charité has obtained an ethical vote for the study of acute stroke patients using ICG-dye bolus technique. UCL received the ethical approval to study hypoxic-ischaemic brain injury in newborn infants. INNCB/PoliMi obtained an ethical approval to investigate patients with photosensitivity and movement disorders.

The different centres - Milan, Berlin, Warszawa and London - established specific experimental protocols to fulfil the aims of the tasks 7.2 (measurement in healthy subjects) and 7.3 (measurement in patients).

A common experimental protocol for the investigation of tdNIRS in healthy subjects was introduced and standardized between institutions. The aim of this experimental design is to provide data, based on identical study-like protocol, from the different institutions with different tdNIRS-systems and to mutually exchange the data between institutions for data analysis and comparison. The harmonized protocol represents simple finger tapping paradigm (motor task) to examine the task-related hemodynamic response over the contralateral motor area using tdNIRS.

Partners involved: P5 INNCB, P6 Charité, P3B UCL_IWH, P8 MUW

Task 7.2: Measurements on healthy adult volunteers

For the harmonized experimental protocol (identical design across centres), INNCB/PoliMi, Charité/PTB, MUW/IBIB PAN and UCL_MPB/UCL_IWH collected data from healthy subjects and analyzed the data sets focusing on the cross-centre comparability. The experimental centres exchanged their results of the stimulation paradigm in healthy volunteers. Common data analysis tools were provided and a consensus was reached regarding common analytical parameters, procedures and resulting parameters. Generally, the results of the different tdNIRS systems revealed comparable results regarding the localization and pattern of the hemodynamic response parameters.

The feasibility to simultaneous co-register tdNIRS together with EEG was successfully tested in separate visual and motor study paradigms from the centres of Milan (INNCB/PoliMi) and Berlin (PTB/Charité). Both tasks elicited a stimulus-related increase in HbO and decrease in HbR over the measured sensorimotor region and resulted in known electrophysiological signatures without any instrumental interference between EEG and tdNIRS instruments. Aside this, a trial-by-trial coupling of EEG (electrophysiological) and NIRS (hemodynamic) patterns has been demonstrated for the visual and motor paradigms. In another multi-modal study PTB/Charité successfully tested the long-term capabilities of tdNIRS instruments by investigating the influence of visual stimulation on sleep stages during a complete sleep period/night in healthy subjects. The results show robust hemodynamic signal changes even after hours of continuous recordings and demonstrate the bedside and monitoring feasibility of tdNIRS technique.

IBIB PAN/MUW successfully demonstrated the bolus perfusion measurements in healthy subjects using various experimental protocols. IBIB PAN/MUW observed that a low ICG dose is sufficient to observe a clear signal of inflow and washout of the dye.

Partners involved: P1A PoliMi_FIS, P2 PTB, P3A UCL_MPB, P4 IBIB PAN, P5 INNCB, P6 Charité, P3B UCL_IWH, P8 MUW

Task 7.3: Measurements on patients

MUW/IBIB PAN measured brain hemodynamics in patients with acute neurological disorders with tdNIRS in combination with injection of ICG and analysis of diffuse reflectance and fluorescence. MUW/IBIB PAN confirmed that the bolus-tracking method based on ICG injection provides information on blood perfusion of the brain. Signals obtained in patients with reduced blood perfusion (brain oedema) and in patients with cessation of cerebral blood flow (brain-dead patients) showed statistically significant difference in comparison to signals obtained from healthy volunteers. It was shown that the signals obtained in posttraumatic intracerebral hematoma patients are highly dispersed which is related to the heterogeneity of the composition of tissues under investigation. MUW/IBIB PAN demonstrated that the signals obtained in patient with blood brain barrier disruption have a highly reduced washout of the dye, suggesting that the technique based on ICG can be applied in clinical assessment of blood brain barrier.

PTB/Charité investigated the bolus perfusion in acute stroke patients using bedside tdNIRS. tdNIRS revealed a lagged bolus response in the stroke-affected hemisphere compared to the contralateral (unaffected) side. Charité/PTB showed that that the malfunctioned perfusion in acute stroke patient using ICG bolus technique can be successfully monitored by means of tdNIRS technique. Moreover, the relative normalization of perfusion after stroke-oriented therapy can be successfully monitored using tdNIRS technique. For both oxygenation changes in healthy subjects and bolus perfusion measurements

in acute stroke patients, it was shown, that the variance parameter of DTOF provides the most robust, cortex-related signal compared to other analytical moments.

UCL successfully evaluated their time-resolved optical tomography system in the neonatal intensive care unit. The response of the normal and pathological brain to sensory stimuli was tested in newborns. In newborn infants UCL revealed evidence of a steal effect, when blood from surrounding vessels is recruited to supply the activated region. This may be more apparent in infants than in adults due to the immaturity of the vascular system.

INNCB/PoliMi investigated patients with photosensitive epilepsy using tdNIRS and observed a hemodynamic response in the occipital region to visual stimulation. INNCB/PoliMi assessed the oxygenation response in patients with movement disorders using tdNIRS in combination with EEG and peripheral signals. Within subjects/patients, consistent NIRS, fMRI, TMS-brain mapping and EEG signatures have been reported. Comparable hemodynamic responses in motor areas were obtained for patients with movement disorders and healthy controls. The hemodynamic activations obtained by fMRI and NIRS revealed comparable activations and localizations, demonstrating the reliability of NIRS technique. In an alternating handgrip task it was shown that patients with Unverricht-Lundborg disorder reveal a rather bilateral and broader activation pattern compared to healthy controls, suggesting the harder effort made by the patients to perform this task. Based on the generated data of these patients, INNCB/PoliMi successfully used EEG/EMG signatures as predictors for the NIRS-GLM analysis.

Partners involved: P1A PoliMi_FIS, P2 PTB, P3A UCL_MPB, P4 IBIB PAN, P5 INNCB, P6 Charité, P3B UCL_IWH, P8 MUW

Deliverables:

- D 7.1: Clinical protocols
- D 7.2: Database of Part I clinical studies
- D 7.3: Database of Part II clinical studies

WP 8 Evaluation of novel methodologies

Start month: 1
End Month: 48
WP Leader: P5 INNCB

Task 8.1: Field survey on clinical use of diffuse optical imaging of brain

A systematic review of papers regarding the use of NIRS in selected clinical fields (stroke, hypoxic-ischemic brain injury and haemorrhage in newborns, epilepsy and movement disorders, traumatic brain injury) was performed. The results of the review included a detailed table with the technical and clinical features specific for the different pathologies and used to define the clinical protocols.

In summary, the literature review showed that:

a) In previous studies performed in patients with epilepsy (reviewed by INNCB) NIRS was mostly used to evaluate the dynamic hemodynamic changes associated with seizures, the lateralization of epileptic focus and of speech cortical area during pre-surgical testing. The main limits appeared to be its poor temporal correlation and the comparability with EEG findings, while the NIRS

topographic information was comparable with that of fMRI, although with a lower spatial resolution.

b) In previous studies performed in patients with stroke (reviewed by Charitè) NIRS appeared to be appropriate to measure the perfusion delay and the immediate changes in oxygen saturation; it was well applicable for intraoperative monitoring and helpful for investigating post-stroke cortical activation and perfusion-reperfusion deficit at the bed-site.
c) In traumatic brain injury (literature reviewed by MUW) NIRS was useful in early recognition of intracranial hematomas and it was sometimes more suitable than other commonly applied procedures. Deeply located lesions, bilateral abnormalities and small hematoma were sometimes difficult to recognize. The addition of indocayne green (ICG) bolus was found to have a great potential in measuring cerebral blood flow.
d) Studies performed in newborns' brains (reviewed by UCL_IWH) showed great diagnostic potential due to the low thickness of the skull and lower scattering coefficient.

Results of literature review suggested that NIRS actually can be a suitable diagnostic tool in alternative to other imaging techniques, namely for studies in impaired and paediatric patients. The major disadvantages were the limited penetration of the light, making difficult to collect data from subcortical structures, the low spatial resolution with respect to fMRI and possible influences of extra cerebral tissue.

Partners involved P1A PoliMi_FIS, P2 PTB, P3A UCL_MPB, P4 IBIB PAN, P5 INNCB, P6 Charité, P3B UCL_IWH, P8 MUW, P1B PoliMi_BIO

Task 8.2: Indications for clinical use of time-domain diffuse optical imaging of brain

In order to provide indications, recommendations and perspectives for the upcoming clinical use of the time-resolved NIRS (trNIRS), the partners discussed and approved protocols and recording procedures in agreement with that proposed in WP7 and delineated during the periodical meetings between technical and clinical partners. These protocols were at first applied by each partner in healthy subjects during the first measurement campaign (months 7-24). Outcomes of tests and experiments on tissue phantoms (WP1, WP2, and WP4), results from measurements and accomplishments on healthy volunteers (WP6 and WP7) were critically reviewed and evaluated to highlight the best achievable methodologies, to identify the limits and the critical points and to propose appropriate correction of protocols, recording procedures and signal processing and analysis. The specific results and observations from the different partners are the following:

UCL_CS has developed and evaluated some methods to improve the reliability of imaging activations in the neonatal brain using anatomical information and applying the layered model and boundary element method to reconstruct activations directly onto the cortex. In collaboration with PTB, UCL_CS developed methods to estimate optical parameters for different tissue classes of adult head using combined time-domain optical data and anatomical information from MRI, and the approximation error theory. This allowed expanding the methodology to infant subjects and to improve optical measurements.

INNCB, PoliMi_FIS and PoliMi_BIO performed studies aimed at evaluating simultaneous EEG-fMRI and EEG-fNIRS recordings in voluntaries and patients with cortical myoclonus due to Unverricht-Lundborg disease (ULD) obtaining the evidence of a good comparability of the topographical location between electrophysiological and hemodynamic measures (Center of gravity evaluated with TMS, maximum of both trNIRS and EEG motor related changes). Moreover, they evaluated the simultaneous EEG and NIRS changes occurring during intermittent visual stimulation in healthy subjects and in patients with photosensitive epilepsy. These studies demonstrated the usefulness of (EEG/EMG informed) GLM analysis for NIRS data in healthy subjects and patients with photosensitive epilepsy and

movement disorders. Critical points to be solved concern the comfort of subjects during long lasting stimulus protocols, and the optimisation of signal-to-noise ratio.

Charité and PTB used the fNIRS system developed by PTB to evaluate simultaneous EEG-NIRS acquisition during motor task (finger tapping, hand clenching) and during 8 Hz flicker light (including short and long-term measurement). They successfully demonstrated the feasibility of perfusion measurements with the prototype of a trNIRS system and measurements using time-domain diffuse optical imaging revealed robust cerebral activations for motor and visual areas. This method, increasing the capability of better separating extra cerebral and cerebral signals allowed to overwhelm a critical point for clinical applications and favours trNIRS as a potential monitoring tool for clinical use.

In addition, PTB performed a study in collaboration with UCL and the Free University Berlin on prefrontal activation during continuous performance task on healthy subjects, demonstrating that functional activation induced by cognitive tasks can be assessed by trNIRS. However, while they obtained consistent results with NIRS signals using motor and visual stimuli, they found residual problems during continuous performance task.

IBIB PAN and MUW performed a study in health and post-traumatic brain injury subjects; moreover, they included patients with defined brain death. They set-up the instrument and the optode array in a suitable way for applications in a critical clinical environment. Their system significantly improved the recordings but critical points remain concerning the quality of the data and the possibility to obtain online information.

The main results obtained during the first measurement campaign indicate that:

a) trNIRS technology is easily applicable in a clinical context, except in the presence of large postural changes.
b) trNIRS approaches and improvements used to detect and characterize the hemodynamic changes associated with the proposed tasks demonstrated the technical feasibility of the procedures. At the same time, the partners focused some critical points dealing with the optimization of optode fixation and the experimental setting with the aim of reaching the optimal comfort of subjects.
c) Statistical analysis (including: GLM, ANOVA, non-parametric test) indicated a good correspondence between trNIRS results and those obtained with other techniques (EEG, fMRI) in terms of topography, temporal pattern and amplitude.
d) As far as the analysis software is concerned, the partners indicated that a critical point for the use of trNIRS in the clinical environment is the development of tools for the signal online evaluation.
e) A small but non-negligible percentage of negative results with trNIRS recordings need to be further investigated.

Partners involved: P1A PoliMi_FIS, P2 PTB, P3A UCL_MPB, P4 IBIB PAN, P5 INNCB, P6 Charité, P3B UCL_IWH, P8 MUW, P9 ILM, P3C UCL_CS, P11 UniFi, P1B PoliMi_BIO

Task 8.3: Perspectives for clinical use of time-domain diffuse optical imaging of brain

In order to provide perspectives for the future development in specific clinical fields of trNIRS methodologies based on time-domain diffuse imaging, each group evaluated critically the results obtained in patients with different neurological disorders (epilepsy, stroke, brain injury) and in infants.

Generally, trNIRS was well applicable in all subjects (healthy or affected by the selected pathologies) with restrictions resulting from the rather long preparation. With respect to the concurrently recorded techniques, data revealed significant convergence in the temporal and topography patterns. Comparison of

multimodal procedures performed in subjects during motor tasks, including EEG, NIRS, fMRI and transcranial magnetic stimulation assisted by neuronavigation, gave rise to coherent results. The location of hemodynamic changes, revealed by trNIRS and fMRI, largely overlapped.

The main diagnostic benefits obtained by the novel optical methodologies based on time domain diffuse imaging developed within the project related to patients with acute vascular accident and neonatal brain insults because in this pathological field trNIRS was especially suitable to detect fast hemodynamic changes endowed by clinical and diagnostic significance and allowed repeated evaluation at the bed-site. Therefore, trNIRS revealed real-time transient hemodynamic changes actually undetectable by other diagnostic methods.

The application of advanced methods of data processing algorithms and signal analysis techniques significantly improved the results in some cases, but was rather time-consuming and difficult to apply in a diagnostic clinical setting. It is expected that the optimization of measurement methods, analytical algorithms to process the signals will allow obtaining further improvement in data quality and interpretation.

The main critical points remained the optode placement and stability of the recording settings. Moreover, a miniaturization of the trNIRS devices, the implementation of a user-friendly interface and the development of online signal processing tools should further improve the applicability in a clinical setting and in acute disorders.

The results obtained on patients with severe brain vascular disorders suggest the concrete applicability and usefulness of the time-domain trNIRS to assess brain perfusion disorders in intensive care units. This can be the topic of multi-centric clinical trials based on the specific protocols defined within the project. More extensive application in patient series of the newly implemented trNIRS technologies will sustain a larger and more selective application, namely in patients with acute disease implicating dominant hemodynamic impairment.

Partners involved: P1A PoliMi_FIS, P2 PTB, P3A UCL_MPB, P4 IBIB PAN, P5 INNCB, P6 Charité, P3B UCL_IWH, P8 MUW, P9 ILM, P3C UCL_CS, P11 UniFi, P1B PoliMi_BIO

Deliverables:

- D 8.1: Field survey on clinical use of diffuse brain optical imaging
- D 8.2: Indications for clinical studies or technical development of Part II
- D 8.3: Perspectives for clinical use of time-domain diffuse optical imaging of the brain

Potential Impact:

Impact on Non-invasive Prediction, Diagnosis, Monitoring, and Prognosis

The brain is by far the most complex organ in the human body and the least well understood. Until relatively recently, it was only possible to identify the function of specific regions of the brain via observation of the effects of disease or trauma or direct intervention within distinct anatomical sites. Although monitoring of electrical activity in the human brain has been performed clinically for several decades, the advent of functional imaging techniques during the past twenty years is providing new knowledge about brain function and its development, and enabling new approaches to be developed in the diagnosis and treatment of brain pathology. Optical imaging provides many important advantages over other non-invasive functional techniques, such as functional magnetic resonance imaging (fMRI), nuclear medicine, and magneto-encephalography (MEG): it is non-ionising, so can be used repeatedly or continuously without risk to the subject; it is portable, so can employed at the bedside; it exhibits direct sensitivity to blood flow and oxygenation; and it is relatively inexpensive.

Moreover since it does not interfere with other diagnostic measurements, it can be used in a multimodality approach. NEUROPT has the potential for a major impact on several different patient groups.

For patients with serious neurological conditions such as stroke or brain injury resulting from severe trauma, optical techniques offer a means to diagnose extent of functional impairment, monitor progress of the condition, and improve prognosis for recovery. Monitoring can be performed continuously and at the bedside, and without interfering with routine critical care. The ability to assess brain function non-invasively will also aid the development of therapeutic procedures (such as new drugs or new forms of surgical intervention) by enabling changes over a long period of time to be recorded.

Sufferers of epileptic seizure and dystonia are other groups of patients on whom this project can have a substantial benefit. Optical methods have the unique potential to detect transient changes in brain blood volume and oxygenation associated with paroxysmal electrical activity, including within deep brain regions that could be missed by electroencephalography (EEG). Monitoring with optical-based techniques thereby has the potential to provide a powerful means of evaluating new drug treatments for these conditions. It has also been reported that blood flow changes might occur before an epileptic seizure. In future prospective, on the basis of the outcomes of the project, a small portable optical dedicated device could alert the patient of the incoming seizure with great benefit for his/her life quality.

Optical imaging is also being developed as a means of imaging the brain of newborn infants, particularly those at risk of hypoxic-ischaemic encephalopathy, which is a major cause of permanent disability in very preterm infants. Visualisation of blood volume and oxygenation within the brain could make a major impact on the management of critically ill infants in intensive care, and on the development of therapeutic methods for preventing permanent brain damage (such as brain or body cooling). Optical techniques can also provide an insight into neurodevelopment during the first few weeks or months of life, and improve our understanding of the pathophysiology of brain injury.

List of Websites:
http://www.neuropt.eu

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