Quality control and assurance in functional near infrared spectroscopy (fNIRS) experimentation

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Abstract. Functional near infrared spectroscopy (fNIRS) is a rapidly developing neuroimaging modality for exploring cortical brain behaviour. Despite recent advances, the quality of fNIRS experimentation may be compromised in several ways. Firstly, by altering the optical properties of the tissues encountered in the path of light. Secondly, through adulteration of the recovered biological signals (noise). And finally, by modulating neural activity. Currently, there is no systematic way to guide the researcher regarding these factors when planning fNIRS studies. Conclusions extracted from fNIRS data will only be robust if appropriate methodology and analysis in accordance with the research question under investigation are employed. In order to address these issues and facilitate the quality control process, a taxonomy of factors influencing fNIRS data have been established. For each factor, a detailed description is provided, and previous solutions are reviewed. Finally, a series of evidence-based recommendations are made with the aim of improving consistency and quality of fNIRS research.

1. Introduction

In functional Near Infrared Spectroscopy (fNIRS), the quality of the experiment and of the recovered haemodynamic signals may be compromised in several ways, including modulating the subject’s cognitive response, distortion of the recorded signals and/or affecting the optical properties of tissues thereby altering pathlength. There have been many review articles detailing fNIRS principles, technological advances, system design and/or applications (Villringer and Chance, 1997; Strangman et al., 2002; Rolfe, 2000; Hoshi, 2007; Gibson and Dehghani, 2009; Lloyd-Fox et al., 2009). However, there have been limited efforts at producing a unified evidence-based framework to ensure the quality of fNIRS experimentation and help guide the novice researcher.

The motivation of this paper is to summarize the factors that may influence the quality of fNIRS experimentation. In addition, evidence-based procedures designed to enhance the quality of fNIRS
Quality control in fNIRS experimentation are evaluated. This systematic framework for best practice is designed to assist new researchers to appropriately plan, design and evaluate the results of fNIRS experiments. The rapid developments in multimodal imaging (Hoshi, 2007) means that this framework is also likely to benefit researchers experienced at other neuroimaging techniques such as electroencephalography (EEG) or functional magnetic resonance imaging (fMRI). The framework focuses on optical topography (OT) as this is currently the most relevant modality for functional neuroimaging studies, although many of the principles covered also apply to optical tomography. Ethical aspects and moral implications are considered beyond the scope of this paper even though they have implications for scientific quality.

2. A Taxonomy of Experimental Factors Influencing fNIRS Experimentation

A taxonomy of the methodological factors influencing experimental quality in fNIRS is proposed in Table 1. In the highest taxonomic rank, the following taxa separate the origin of the factors:

- Environmental; intrinsic to the laboratory,
- Instrumentation; regarding the interplay of the illumination and detection configuration
- Mechanical; related to the optode manipulation, positioning and coupling
- Population; as regards cohort demographics and behaviours
- Physiological; concerning the physical and chemical variables related to human physiology
- and Study design and data analysis; involving generic and fNIRS specific decisions regarding protocol and analysis

The manner in which these factors influence experiment quality is depicted in Figure 1. For each of these factors (1) we state the evidence for the problem, (2) review solutions and (3) whenever possible suggest procedures to alleviate the problem.

![Figure 1](image.png)

**Figure 1.** Pathways for how each factor class may compromise experiment quality. Continuous lines link factors to consequences. Dashed lines represent strong interactions between factors themselves.

3. Environmental Factors

3.1. Ambient Light

Optodes refers to the set of transducer, immobilisation polymer and instrumentation including the optical fibre and light source that makes the optical sensor. Poor shielding and/or coupling between optode and skin permit ambient light to reach the detectors increasing the optical power or irradiance at the sensor. Optode shielding schemes limit the ability of ambient light to reach the photodetectors (Lloyd-Fox *et al.*, 2009). Solutions incorporated into devices to reduce contamination by ambient light include the use of long pass filters (Cope and Delpy, 1988), lock-in amplifiers (Coyle *et al.*, 2004), differential detection
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(Lee, 2004) and embedding sensors in foam (Bozkurt et al., 2005). Sensitivity to ambient light can be reduced by conducting experiments in a dimmed room, e.g. (Hoshi et al., 2005; Holper et al., 2009; Schroeter et al., 2003), and further attenuated by using a light tight bandage (Wyatt et al., 1990) or covering the sensors with a dark felt or cloth (Hoshi et al., 2005; Meek et al., 1995; Obrig et al., 2002).

3.2. Room Conditions
Electronic instrumentation works optimally at certain temperatures, levels of humidity and ventilation. Minimizing temperature fluctuations during the experiment reduces system drift and ensures stability of the measuring system (Schmidt et al., 2000; Haensse et al., 2005). Manufacturers of OT systems, such as HITACHI, recommend installation and use at controlled temperatures and humidity conditions so that equipment operation is stable. In addition, extreme room conditions may influence subject’s comfort and performance. Some investigators report their laboratory temperature (22o-24o) and humidity conditions (40%-50%) and methods of ventilation (Tanida et al., 2007; Kudo et al., 2008). In general, experiments should be conducted at room temperature.

4. Instrumentation Factors

4.1. Illumination System
A range of commercial and in-house systems for fNIRS application have been described (Franceschini et al., 2006; Yamashita et al., 1998; Everdell et al., 2005; Bozkurt et al., 2005; Haensse et al., 2005; Cope and Delpy, 1988; Schmidt et al., 2000; Siegel et al., 1999). Each system possesses a unique illumination and detection configuration. A schematic diagram of a commercial OT-fNIRS system is illustrated in Figure 2.

Figure 2. Schematic representation of a functional near infrared measurement system.

4.1.1. Cross-talk. To recover more than one chromophore (e.g. oxy-Hb and deoxy-Hb), fNIRS capitalizes on the distinct absorption curves of the chromophores to be recovered. The incorrect separation of chromophore changes is known as cross-talk (Uludag et al., 2002; Strangman et al., 2003). Cross-talk is
mainly affected by wavelength selection, but also by errors in the extinction coefficient used, and the stage at which instrumentation noise and motion artefacts are eliminated (Ulad et al., 2004; Sato et al., 2004; Yamashita et al., 2001; Huppert et al., 2009). To minimize the degree of cross-talk, the growing consensus is to utilize one wavelength at 830nm and another one between 660 and 770nm (Gibson and Dehghani, 2009).

4.1.2. System drift and optode calibration. System drift is due to low frequency noise introduced by an electronic instrument which results in poor signal-to-noise ratio for repeated measurements. Optode calibration methods regulate the strength of the light sources, automatically adjust the gain of the detectors, determine initial optical properties and boundary conditions, and remove errors from model mismatch. A number of calibration algorithms have been proposed for all the three NIRS modalities; time- resolved, e.g. (Hebden et al., 2003), frequency domain, e.g. (Li and Jiang, 2004) and continuous-wave, e.g. (Stott et al., 2003). For continuous wave systems, a simple normalization may suffice as an alternative to calibration procedures (Huppert et al., 2009). Linear detrending is a simple solution to eliminate system drift, consisting of fitting a first degree polynomial to baseline samples and subtracting it from the signal. Optode calibration methods ensure optimal gain of receptors, and in addition they can partially compensate for gradual movement of the optodes, and ambient light contamination.

4.1.3. Laser heating time and life. Light sources in NIRS applications employ either laser or light emitting diodes (LED) sources. Cold lasers do not perform optimally. Thus, operating with cold lasers results in a reduced SNR and interference with optode calibration. Reported laser warm-up times range from 30 minutes up to 10 hours (Haenese et al., 2005; Schmidt et al., 2000). Thermoelectric coolers permit thermal control of the laser for optimum performance (Williams, 2001). In addition, as the lifetime of the laser expands their luminosity fades and their performance decreases. It is advisable to switch on the lasers at least 30 minutes prior to data acquisition.

4.2. Propagating Fibres. 
The type, material, width and length of the fibres propagating the illumination to the tissue may distort light profile and deviate from nominal measurement wavelengths. The propagation velocity of light travelling through the fibre is wavelength dependent, resulting in wavelength specific delays. The more the illuminating profile differs from the nominal, the greater the need for stray-light rejection (Siegel et al., 1999). Longer fibres can increase subject mobility, and the attenuation suffered by light in short distances within a laboratory may be neglected. Although glass fibres are expensive, they are more flexible, weigh less and provide improved optical measurements than other materials (Lloyd-Fox et al., 2009).

4.3. Laser Safety.
Safety in fNIRS systems imposes restrictions on the way the NIRS imaging devices are used. The International Electrotechnical Commission’s (IEC) report states that light in the wavelength range 400nm to 1400nm has the potential to cause photochemical and febrile damage to the retina, and cataract, as well as to inflict retinal and skin burns (IEC, 2007).

4.3.1. Injury to the skin. NIR light is non-ionising but it is transferred to thermal energy following absorption (Ito et al., 2000). The combined effect of radiated and conducted heating characterizes the increase in tissue heating, which quickly decreases with depth and deviation from the irradiation point. Maximum permissible exposure (MPE) of the skin against laser radiation is 3.3mW/mm2 for 2-wavelengths, so optical fibre output is permitted up to 31.4mW. However, the exact limits of maximum radiation depend on many factors including emission wavelength, light coherence, exposure time, area being illuminated, light beam characteristics and the absorption and scattering properties of the tissue, as well as the subject’s skin tolerance, e.g. neonates and albinos are special groups at risk. Exceeding safe power limits will result in tissue heating and in extreme cases in thermal necrosis (Siegel et al., 1999).
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Commercial devices often work well below the MPE threshold. For instance, the ETG-4000 (Hitachi Medical Corporation) optical fibre output is set to 3mW that is 1/10 of the MPE. For high precision analysis, thermally induced alterations of the optical properties of the tissue can be modelled with energy transport models.

4.1.2. Injury to the eye. Eye lens directs the light beam into the fovea, which receive a potentially harmful stronger irradiance. Most fNIRS devices operate at power levels consistent with Class 1M lasers (safe as the blink reflex prevents ocular exposure for more than 0.25s) according to IEC safety standard (IEC, 2007). However, caution should be taken to avoid inadvertent eye exposure, since the threshold to avoid ophthalmic injury is substantially lower than that for the skin. It is desirable that the lasers are not switched on until the optodes are in contact with the subject’s scalp, but volunteer discomfort and laser warm-up times may prove this unfeasible. An alternative strategy is to ask subjects to close their eyes or to use eye protection during optode placement.

4.4. Detection system

Scintillation light detectors commonly employed in fNIRS are either photomultiplier tubes (PMT), conventional silicon photodiodes (SPD) or avalanche photodiodes (APD). Regardless of the scintillator and the mode of operation of the detector (pulse or current), the output from the sensor may become saturated due to the high optical power or irradiance -commonly by exposure to ambient light-, the applied voltage bias, saturation of the circuit parts, ambient electrical/magnetic noise, or radio waves emitted by devices such as cell phones. For time resolved apparatus, power supply stability, optical reflectance, data acquisition efficiency, temporal accuracy and laser pulse stability may also adversely influence light detection (Schmidt et al., 2000). In a two wavelength system reconstructed with the modified Beer-Lambert law, if only one wavelength is saturated the concentrations changes in oxygenated and deoxygenated haemoglobin are related by a negative constant, an effect referred to as ‘mirroring’. If both wavelengths are saturated, changes in concentrations become zeroed, an effect that we call ‘apparent non-recording’. Figure 3 illustrates common artefacts induced as a result of detector saturation.

Figure 3. Detector saturation artefacts. Example of experimental data showing changes in hemoglobin species HHb(blue line) and HbO2 (red line) under saturation artefacts. The shaded patches correspond to self-pace surgical knot-tying task blocks. The first stage is only affected by the saturation at one of the acquisition wavelengths, and the mirroring effect is clearly observable. From there onwards, the detector also gets saturated at the second wavelength and a non-recording effect appears.

Strategies to detect saturation artefacts include thresholding raw light data stream before conversion to chromophore concentration (Huppert et al., 2009) or spectral analysis (Blasi et al., 2007). Capitalizing on the numerical solution of the modified Beer Lambert law (MBLL) differential system of equations, our practice is to apply a multiscale cross-correlation algorithm to detect saturation. In systems where a large variation of source-detector distances is permitted, the dynamic range of the intensity of the emergent light will be very large. In this instance, variable optical attenuators are necessary to avoid
saturation or even damage to the detectors (Schmidt et al., 2000; Haensse et al., 2005). Huppert et al (Huppert et al., 2009) recommend eliminating instrumental noise before conversion of light to haemodynamic data so the error does not propagate. Channels suffering from saturation artefacts should be identified, and this data rejected from further analysis.

5. Mechanical Factors

5.1. Interoptode Distance
The diffuse nature of photon migration within the tissue limits the depth of light penetration (Boas et al., 2004; Franceschini and Boas, 2004). Depth sensitivity depends on the illumination strength and optical properties of the tissues in the light path including the concentration of the chromophores. Infrared light can only penetrate up to 8 cm in neonates (Wyatt et al., 1990) and 7 cm for adults (Villringer and Chance, 1997). For planar imaging, relying on backscattered photons, the depth achieved is a function of the interoptode distance and the fibre orientation with respect to the tissue entrance plane (Thilwind et al., 2009). If the interoptode distance is too small, the acquired signal will originate from extra-cerebral structures. Conversely, if source and detector are widely separated i.e. distances exceeding 40-50mm, then relatively little light reaches the detectors and signal quality is degraded. If beam entrance is perpendicular to the tissue, a typical source-detector separation when measuring the brain haemodynamics in adults is 30mm, e.g. (Watanabe et al., 1996; Okada and Delpy, 2003b; Sato et al., 2006b; Obata et al., 2003), which is also optimum for measuring the fast optical signal (Gratton et al., 2006; Franceschini and Boas, 2004). At the 30mm distance the contribution of the gray matter to the light absorption has been estimated in the order of 20%-30% (Toronov et al., 2000). Smaller source-detector separations are also popular, e.g. 25mm (Zee van der et al., 1992) especially in infants (e.g. 20 mm).

5.2. Geometric configuration of optodes
The position and configuration of light sources and detectors on the scalp determine the cortical region(s) under surveillance and limits the accuracy and resolution of the reconstructed image. At a given source-detector separation paths closer to the surface are shorter and denser than deeper paths. Overlapping geometries where several channels interrogate the same region, and high density arrays providing multidistance measurements provide better image quality and spatial resolution than non-overlapping single distance geometries (Boas et al., 2004; Dehghani et al., 2009b; Yamamoto et al., 2002; Saager and Berger, 2008). However, with single distance non-overlapping geometry the topographic images may be recovered by simple interpolation. Explicitly reporting optode arrangement is a common practice among investigators.

5.3. Optode-Scalp Coupling
Optode-skin/scalp coupling refers to the tightness and stability of the optode’s position with respect to the scalp. Variations in this coupling result in changes in the detected light intensity. Gradual optode movement leads to slow changes that may mistakenly be interpreted as system drift. Abrupt optode movement, also referred to as “body movement” artefact, manifest themselves as large sudden changes in chromophore concentration, distinct from genuine changes due to cortical activity and more irregular than system noise (Sato et al., 2006c).

5.3.1. Headgear. The headgear in which the optodes are mounted should ensure good optode-skin coupling and subject comfort. A variety of devices to house the NIR optodes have been described including thermoplastic shell or splint molds (Takahashi et al., 2000), steel tubes affixed to a metal frame (Toronov et al., 2000) and aluminium shells (Blasi et al., 2007). Mechanical stabilization of the optodes has been attempted by anchoring the optical fibres to a backpack or harness (Huppert et al., 2009), inserting foam (Bozkurt et al., 2005), employing integrated source detector bundles (Hebden et al., 2003), prism-ended optodes (Lloyd-Fox et al., 2009), head rests (Meek et al., 1995), and/or Velcro tape (Franceschini et al., 2006). In general, whilst higher pressure between optodes and skin provides more
stable coupling, excessive pressures induce volunteer discomfort or at worse skin necrosis (Edwards, 1995). The excessive pressure can be eased by means of spring loaded optodes. Index matching gels are used to enhance the coupling with the fibers in other optical applications, but to our knowledge, these are not in widespread use in functional NIRS studies. Despite enhancing stability, headgear alone is unlikely to completely eliminate all optode movement artefacts.

5.3.2. Optode movement. Optode calibration methods may alleviate the signal contamination induced by gradual optode movement but will still fail to compensate for the abrupt changes in NIR signals brought about by a loss of optode-scalp coupling. To pinpoint abrupt optode movement some investigators rely on visual inspection, e.g. (Diamond et al., 2009; Nakano et al., 2009), which is subjective, time-consuming and prone to errors. Generic algorithmic solutions for edge detection such as Sobel’s mask or Laplacian of a Gaussian can provide good sensitivity but low specificity. Algorithmic solutions specific to fNIRS include discarding two consecutive differences in the changes in total haemoglobin larger than a hard threshold (Peña et al., 2003), the use of Haar wavelets (Sato et al., 2006c), PCA truncation (Wilcox et al., 2005), local and global assessment of the variance (Holper et al., 2009; White et al., 2009), ICA over co-located channels (Robertson et al., 2010), Kalman filtering (Izzetoglu et al., 2010) and exploiting negative correlations among Hb species (Cui et al., 2010). Our current practice is to perform visual exploration data integrity checks followed by employing an in-house algorithm based on a soft threshold upon a double exponential smoothing signal model to detect data contaminated with artefact, in order to discard it. Examples of optode movement detection algorithms are illustrated in Figure 4. Signal compensation may be necessary to avoid discarding data from studies with small cohorts. Finally, subtle changes in haemodynamics caused by head motion can be removed using accelerometers and a Wiener adaptive filter (Izzetoglu et al., 2005).

Figure 4. Comparison of different approaches for optode movement detection at different scales. HHb: blue line; HbO2: red line; Total Hb: green line. Units of concentration changes are in μMxcm. Abscise axis represents time courses in seconds. The different rows represent response of different amplitude. The first column correspond to detection by two consecutive large changes (Peña et al., 2003). The second column uses Haar wavelets to look for steps in the signals (Sato et al., 2006c). The third column defines a flexible region using a double exponential smoothing (Orihuela-Espina et al., 2008).
5.4. Optode Positioning, Location and Registration
Accurate positioning of NIR optodes onto the scalp surface ensures that sampled data originates from the cortical region(s) of interest. Conversely, errors in optode positioning or misalignment of optodes can potentially lead to invalid conclusions regarding cortical function. Typically, optodes are guided into position using the International 10/20 system for optode placement, or an equally valid alternative reference in which more cranial positions are defined such as the UI 10/10 or 10/5 systems (Jurcak et al., 2007). Registration permits mapping the location of optode and channels on the scalp surface to underlying anatomical location on the cortical surface. This is extremely valuable for fNIRS which does not incorporate anatomical information per se. Moreover, registration realizes reproducible measurements across subjects, studies and laboratories, and facilitates comparison of data acquired across different neuroimaging modalities.

Whilst the positioning systems are standardized, there is a considerable heterogeneity regarding the range of implementation and solutions for registration. The current gold standard is co-registration with magnetic resonance anatomical data, which involves placing fiducial markers such as fatty pine nuts (Okamoto et al., 2004), vitamin capsules (Hatakenaka et al., 2007) or Beekley Spots® (Gratton et al., 2006) over optode locations such that the cortical region underlying each optode can be determined from individual subject high resolution MRI images. However co-registration may prove costly and difficult especially in infants. An alternative approach is to use a digitizer to determine 3D locations (Singh et al., 2005) which are then projected to onto a brain atlas. Virtual registration negates the need for 3D digitizers (Tsuzuki et al., 2007) although this technique is not in routine use at present. To quantify the discrepancy between the intended cranial marker and the location where the measurement was actually recorded, our current approach is, following 3D position digitisation, to deform a hemi-spheric mesh representing a standard positioning system, and compute the distance from either the real optode location or real channel location to the intended target location, as illustrated in Figure 5. A threshold chosen upon the spatial resolution and the interoptode distance is then used to justify data rejection.

Figure 5. Optode registration. A hemi-sphere representing a standard location system e.g. 10/20, UI 10/10 or 10/5 is deformed to fit five control points (red dots and labels). Distances can then be computed in real world units. Under the assumption of a one-to-one match between the standard locations and associated cortical regions, the imaged cortical area can be established. (a) An hemi-sphere mesh (semi transparent yellow mesh) yet to be deformed; (b) Sagittal (Nz-Iz) –blue- and coronal (T9-T10) –red- axes and the 0%, 5% and 10% axial reference curves; (c) Mesh deformed according to the 3D digitized location of five control points (Nz, Iz, T9, T10 and Cz); and (d) An example on real data showing the 3D locations of optodes (blue circles), estimated channels positions (red squares) and some target standard locations (magenta dots).
Capitalizing on the basis that probabilistic cortical anatomy underlying each standard location has been established unequivocally (Okamoto et al., 2004), some authors do not report any registration effort (Herrmann et al., 2008). Others report the registration for a subset of the cohort assuming internal positioning consistency (Leff et al., 2008a) or occasionally the results for the entire cohort (Gratton et al., 2006). Neglecting to perform and report registration should be discouraged. It is preferable to report the registration technique, and the degree of misalignment between intended and actual channel locations.

6. Population Factors

6.1. Demographics

Cohort selection criteria i.e. inclusion and exclusion, are defined for both safety and scientific reasons (Ottevanger et al., 2003). In group studies, investigators should aim to match the groups to reduce the effect of demographic confounders. Restriction of eligibility makes extrapolation hazardous and increases the complexity of the experiment. Exclusion and inclusion criteria should be described in detail.

6.1.1. Age. Senescence induced cortical atrophy results in changes in the tissue optical properties, which in turn affect the depth of penetration (Svasaand and Elligsen, 1983), optical pathlength (Kameyama et al., 2004), partial volume and cross-talk (Schroeter et al., 2003). In addition, cortical responses in older subjects have been observed to be less pronounced versus their younger counterparts (Herrmann et al., 2006; Mehagnoul-Schipper et al., 2002). The age range or mean age of the recruited cohort and/or groups of interest must be reported. If significant age differences exist between groups of interest then the effect of age should be considered as a confounding or independent factor (Herrmann et al., 2006).

6.1.2. Gender. Gender reorganizes brain activity (Kameyama et al., 2004; Herrmann et al., 2006). Investigators commonly report the sex distribution of the study participants, e.g. (Leff et al., 2008a; Sato et al., 2006b; Plichta et al., 2007a), but few reports describe matching to eliminate sex-related confounds.

6.1.3. Ethnicity. Light absorbed by the scalp is a function of skin colour. Melanin concentrations and composition in the skin and hair greatly varies across race (Alaluf et al., 2002). Moreover, changes in blood pigments are more difficult to observe in the presence of high concentrations of melanin. Notwithstanding, reporting ethnicity of the cohorts is uncommon.

6.1.4. Handedness. The dominance of the left and right cerebral cortex for tasks such as spatial cognition, speech and language is related to handedness. Handedness is most commonly evaluated using a validated scale such as the Edinburgh Inventory handedness (Oldfield, 1970).

6.1.5. Past Medical History and Current Medical Conditions. Many studies report that their volunteers are healthy, e.g. (Higashi et al., 2004; Toronov et al., 2000; Mehagnoul-Schipper et al., 2002) and/or have no psychological or psychiatric history, e.g. (Kameyama et al., 2004; Sato et al., 2006b). Many other medical conditions can influence optical signals, for instance by directly altering the CBF or the systemic response, causing cognitive impairment and/or inducing neurodegeneration, e.g. cardiac diseases, diabetes mellitus, HIV/AIDS, migraine, and gestational hypertension disorders. Vasodilator medication can help to normalize CBF in hypertension (Pieniążek et al., 2001).

6.2. Measurement Day Particulars

6.2.1. Stimulant Intake. Stimulants alter the way in which the brain responds to stimuli. Caffeine increases metabolism while at the same time induces cerebral vasoconstiction, decreases the CBF and modulates brain activity (Higashi et al., 2004; Dager and Friedman, 2000). Nicotine increases CBF and, when combined with caffeine, may result in increases in heart rate and blood pressure, i.e. altering the systemics (Dager and Friedman, 2000). Cerebral autoregulation may maintain CBF in the face of moderate and even acute alcohol intake but alcohol may alter certain higher order brain functions (Obata
et al., 2003). Other drugs have the potential to confound haemodynamic responses (Ladewig et al., 2002; Hasan et al., 2009). Effects of chronic or sustained abuse of certain substances may transcend the day of intake. Experimenters should control for the intake of stimulants by the study cohort. Our practice is to request that participants refrain from drinking alcohol and ingesting caffeine for 24 hours prior to data acquisition.

6.2.2. Attention. Attention regulates the activity of brain circuits (Herrmann et al., 2008). Noise in the laboratory may distract the subject, divert their attention from the task at hand and at worse confound imaging data (Abdelnour and Huppert, 2009). Physical and psychological fatigue can further modulate the brain response (Suda et al., 2009; González-Alonso et al., 2004). Insufficient attention to the task is common when working with infants who may cry, refuse to wear the probes or simply fail to attend to visual stimuli (Taga et al., 2003; Watanabe et al., 2008). Maximizing cooperativeness during data acquisition is essential. Solutions include ensuring that background noise is kept to a minimum by conducting the experiment in a quiet room. Using alternative tasks during rest periods may help to maintain attention and focus. Data acquired when attention to the stimulus is deemed insufficient or unsatisfactory should be discarded.

Anticipatory activation may be generated before repeated predictable events (Nakano et al., 2008) or as a result of anxiety (Morinaga et al., 2007).

7. Physiological Factors

7.1. Neurovascular Coupling

Neurovascular coupling describes the way in which neuronal activity translates into changes in CBF, cerebral blood volume (CBV) and regional cerebral metabolic rate of oxygen (CMRO_2). There exist a number of models for approximating the CBF, CBV and CMRO_2 from fNIRS measurements (Wyatt et al., 1990; Boas et al., 2003). The relationship between neuronal activation and the vascular response is neither temporally nor spatially constant (Obrig et al., 2002; Devor et al., 2005; Sheth et al., 2004). Habituation, a decrease in the response either neural or vascular (Obrig et al., 2002; Krekelberg et al., 2006), may occur within and across trials and can be sustained from minutes to days (Nakano et al., 2009). Interpretation of measured brain haemodynamics must be made with good comprehension of neurovascular coupling, and the conclusions extracted must be bounded by the assumptions made over this physiological process, such as linearity.

7.2. Systemic Effect

Systemic signals such as arterial pulsation, blood pressure, vasomotion, basal cerebral circulation, respiratory rate, gas exchange, and scalp blood flow are known to influence changes in cortical haemodynamics despite cerebral autoregulation (Elwell et al., 1994; Diamond et al., 2006; Obrig et al., 2000; Elwell et al., 1999; Franceschini et al., 2006). In contrast to the localized response due to the neurovascular coupling, the systemic response influences haemodynamics globally. As illustrated in Figure 6, cortical haemodynamics signals may be contaminated at various frequencies with systemic artefacts. Classical filtering will fail to remove systemic oscillations with overlapping frequencies. Solutions to quantify, account for and/or remove systemic artefacts can be classified as follows;

- blind source separation when no concomitant systemic signal are available or acquired (Zhang et al., 2005b; Katura et al., 2008; Virtainen et al., 2009)
- model based incorporating prior knowledge (Abdelnour and Huppert, 2009; Diamond et al., 2006)
- adaptive filtering using systemic physiological data acquired simultaneously with fNIRS, either by means of multidistance acquisition (Saager and Berger, 2008) or using auxiliar technologies (Kohno, 2007).
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Figure 6. The effect of systemic variables on the haemodynamic signal. The upper plot represents the raw HbO2 signal after reconstruction using the modified Lambert law, but without any further processing. The lower plot illustrates the Fourier transform of this signal to the frequency domain. Peaks for vasomotion, breathing and heart rate can be easily appreciated.

The exact extent to which systemic signals contaminate fNIRS data still remains under investigation (Katura et al., 2006). Whenever possible, it is preferable to eliminate systemic interference to reduce false positives (Tachtsidis et al., 2009).

7.3. Extra-Cranial
Extra-cranial contributions to the signal affecting the optical pathlength include aspects of variable anatomy (tissue and skull thickness) and presence and colour of hair (Okada and Delpy, 2003b; Strangman et al., 2002) – scalp blood flow is considered part of the systemic effect. Extra-cranial contributions vary across subjects and head locations. In frequency-domain NIRS, the concentration changes derived from phase change values are more sensitive to deeper layers, hence naturally minimising extra-cranial contamination (Obrig et al., 2002). Dense hair bearing regions of the scalp decrease optode grip and reduce optode scalp coupling. Dark hair pigmentation and the presence of hair follicles may reduce the intensity of the signal, by as much as 20-50% (Koizumi et al., 1999). The simplest solution is to carefully comb hair away from below the optodes or in extreme cases reject data exhibiting low signal-to-noise ratio secondary to hair obstruction, e.g. (Watanabe et al., 2008; Nakano et al., 2009).

7.4. Intra-Cranial
Intra-cranially, light crosses the dura mater, the arachnoid layer, the cerebrospinal fluid (CSF) and finally the pia mater before reaching the cortex. It is adequate to consider the meninges as a single homogenous CSF layer (Okada and Delpy, 2003b; Hoshi et al., 2005; Custo et al., 2006). Photons are strongly affected by this homogenous CSF layer, influencing the optical pathlength and change the depth of the sensitivity profile (Okada and Delpy, 2003b, a).

8. Study Design and Data Analysis Factors

8.1. Protocol Design
The study design and analysis strategy often go hand in hand and are directly relevant for correct interpretation of results. fNIRS researchers face generic decisions regarding designing task and control paradigms, appropriate randomization, selection of population size, appropriate use of inferential statistics including assumption checking and results interpretation (Ottevanger et al., 2003; Petersson et al., 1999a, b). However, fNIRS investigators face additional decisions regarding specific parameters of the
experiment. Specifically, (i) the data acquisition paradigm, (ii) the number of trial repetitions, (iii) the length and intensity of the stimulus and subsequent recovery periods, (iv) the definition of the rest periods or alternative tasks, (v) the temporal window for baseline/task data analysis, and (vi) whether to analyse only one haemoglobin species, both, or a derivate measure such as total haemoglobin (HbT). In our experience, it is useful to conduct pilot studies to adjust protocol design parameters as well as to identify shortcomings likely to arise during data acquisition.

8.1.1. Data acquisition paradigm. In a block design, similar events are grouped or separated into different data acquisition sessions, whereas in an event-related design, events are mixed and acquired in a single session. The block design is more efficient for detecting differences between stimuli because it maximizes the predictor variance although is more affected by physiological noise and anticipation (Lloyd-Fox et al., 2009; Nakano et al., 2008; Morinaga et al., 2007). Event-related designs are superior at coupling brain activity to specific events, therefore allowing more precise inferences. Event-related designs are useful if the task of interest cannot be repeated rapidly and have been shown to exhibit reliability and reproducibility of the signal at group level (Plichta et al., 2006, 2007b).

8.1.2. Number of trials. The number of trials is a compromise between the signal to noise ratio (SNR), habituation and subject comfort. Single trial designs may be insufficient to yield reliable responses due to poor SNR but effects of habituation can be expected from as early as the fifth trial (Nakano et al., 2009; Lloyd-Fox et al., 2009). In addition, from our own experience, sessions lasting more than 15-20 minutes (including optode positioning and registration time) can become tiresome for adult volunteers.

8.1.3. Length and intensity of the stimulus and subsequent recovery periods. The observed haemodynamic response is dependent on the duration of both stimulus and the inter-trial intervals (Obrig et al., 1997; Toronov et al., 2000). For a long stimulus the HbO2 signal may reach a plateau, that it is maintained until the cessation of the stimulus (Heekeren et al., 1997). If the inter-trial interval is small the pre-stimulation baseline may reflect post-stimulus changes from the previous trial. Longer inter-trial intervals lead to prominent HHb overshooting (Obrig et al., 1997). The intensity and or complexity of the stimulus further modulate the strength of the haemodynamic response and may even determine the recruited brain circuitry (Suzuki et al., 2004).

8.1.4. Definition of the rest periods or alternative tasks. A rest period of complete mental/motor inactivity is desirable to provide a reliable baseline. For visual stimulation, the rest period usually involves switching the monitor to a black screen (Plichta et al., 2006). However, maintaining mental inactivity may be challenging. For example, one cannot enforce inactivity in infants and so alternative tasks must be designed, such as attracting an infant’s attention with animated cartoons during rest periods (Blasi et al., 2007).

8.1.5. Temporal window for analysis. Temporal window selection for data analysis may be the difference between success and failure of detecting brain activity. Researchers often analyze the time to peak of HbO2 or the time to nadir of HHb, e.g. (Watanabe et al., 2008). However, these variables are prone to large inter subject and inter task variation (Obrig et al., 1997). Temporal window selection or period where activation is looked for can be fixed (same onset and duration across all subjects and trials) or floating (variable onset and/or duration incorporate the time to peak or nadir respectively) (Sato et al., 2006b) and can either be aligned with the onset of the stimulus or delayed (usually 3-5 seconds). Furthermore, the selected window may or may not extend beyond the duration of the stimulus itself in order to capture the peak response, thus incorporating rest data as stimulus data. Temporal normalization may be appropriate for self paced tasks before selecting a temporal window for analysis (Leff et al., 2007). Currently, there is a lack of consensus regarding the most suitable temporal window for analysis.
8.1.6. **Haemodynamic signal for analysis.** The classical haemodynamic signature of brain activity as detected with fNIRS is an increase in HbO2 and a concurrent decrease in HHb, together with an increase in HbT. Multivariate analysis is possible but is usually complex. Many authors prefer to address functional questions in terms of only one Hb species, i.e. one variable. The decision of which variable to use is not trivial. HbO2 has been said to be the most sensitive indicator of regional CBF in NIRS measurements (Hoshi et al., 2001), but HHb better reflects the match between oxygen supply and demand (Elwell et al., 1994). Also, physiological noise is more prominent in HbO2 (Obrig et al., 2002). Furthermore, due to cross-talks, the recovery of both signals are to some extent affected by their counterpart. Even when both haemoglobin signals are considered, the statistical analysis is actually performed as two independent univariate analyses, e.g. (Sato et al., 2007; Plichta et al., 2006), rather than being multivariate. Optical neuroimaging is also capable of detecting the terminal enzyme of the respiratory chain, known as cytochrome oxidase (Jöbsis et al., 1977; Rolfe, 2000). Although it is arguably the most specific to brain activity, its measurement is more complicated than that of the vascular parameters, mainly because the amplitude of the signal is at least one order of magnitude smaller than that of haemoglobin (Greisen, 2006).

8.2. **Image Reconstruction**

With fNIRS, changes in light intensity only (continuous-wave), intensity and phase (frequency domain) or time of flight (time resolved) are monitored to reconstruct the cortical haemodynamics. Image reconstruction refers to the problem of recovering meaningful chromophore concentrations from detected light measurements (Arridge et al., 1997). Image reconstruction is critical and ultimately determines the spatial and temporal accuracy of the haemoglobin concentration recovered. The theory or model adopted to solve this inverse problem varies according to the imaging modality and requires a trade off between assumptions made, complexity and computational burden (Arridge et al., 1997; Hebden et al., 1997; Dehghani et al., 2009a).

Concerning OT, the MBLL (Delpy et al., 1988) is almost universally applied to image reconstruction. The MBLL ignores light polarization and assumes elastic scattering, independent effect from the absorbers, monochromatic radiation, a non-changing source detector configuration and a constant homogeneous medium geometry. Due to the unknown scattering properties, the MBLL cannot recover absolute Hb concentration values, but rather changes in concentration upon differential formulation. The differential pathlength factor (DPF) in the MBLL accounts for the increase in the optical pathlength caused by intense scattering of photons in biological tissues (Delpy et al., 1988; Zee van der et al., 1992; Duncan et al., 1995; Sato et al., 2006a; Kohl et al., 1998). The DPF is known to vary with wavelength (Essenpreis et al., 1993), interoptode distance (Zee van der et al., 1992) and penetration depth – for a fixed interoptode distance- (Hemelt and Kang, 1999). A common approximation is to represent the DPF by a single value, e.g. 5.93 for adults and 3.85 for infants (Zee van der et al., 1992), but such a crude approximation has been criticized (Okada and Delpy, 2003b). Other researchers do not apply DPF correction, and work with relative changes in Hb concentration, e.g. (Nakano et al., 2008; Leff et al., 2008a).

8.2.1. **Temporal versus spatial reconstruction.** Reconstruction is usually spatial, not temporal i.e., the solution to the inverse problem is computed at every time point (Zhang et al., 2005a). To directly model the temporal dynamics of the chromophores, a haemodynamic response function (HRF) model must be convolved with the stimulus train. While HRF models are widely applied in fMRI, not until recently has an HRF specific to optical imaging have been proposed (Zhang et al., 2005a; Akin and Bunce, 2003) and some models now accept temporal basis functions as inputs (Diamond et al., 2006).

8.3. **Image Processing and Analysis**

De facto standard processing of fNIRS signals includes low-pass or band pass filtering to remove instrumentation noise, detrending to eliminate system drift and averaging across trials to increase SNR
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(Huppert et al., 2009; Lloyd-Fox et al., 2009). Data integrity checks, or signal assessment, detect and/or eliminate artefacts not rectifiable using such standard processing framework and ensure that only appropriate clean signals are allowed to be analysed further. Approaches to data integrity include visual assessment, or systematic algorithmic checks. Several software packages for fNIRS image reconstruction and signal processing are already available:

- fOSA (function Optical Signal Analysis) (Koh et al., 2007) (http://www.fil.ion.ucl.ac.uk/spm/).
- ICNA (Imperial College Neuroimage Analysis) (Orihuela-Espina et al., 2009).
- NIRS-SPM (NIRS Statistical Parametric Mapping) (Ye et al., 2009) (http://bisp.kaist.ac.kr/NIRS-SPM.html)

A classical dichotomy considers analysis techniques as either hypothesis-driven or data-driven. Well established hypothesis-driven frameworks from other neuroimaging modalities such as the general linear model and its variant statistical parametric mapping are now being adapted for fNIRS application (Plichta et al., 2007a; Koh et al., 2007). New data-driven approaches such as manifold embedding (Leff et al., 2007) and Markovian modelling (Leff et al., 2008b), are expanding the range of analysis options. We favour a combination of analysis strategies, developing new data-driven solutions and validating findings using classical inferential statistics.

9. Conclusions
The quality of an fNIRS experiment and the acquired data may be compromised due to errors in methodology adversely affecting the optical signal. In this paper, we have defined a taxonomy of factors that need to be considered to ensure quality in fNIRS experimentation. Each of these factors have been systematically approached in a three-step strategy; (i) factor description, (ii) evidence-based solutions overview, and (iii) conclusions or recommendations based on the former two.

Effort towards excellence in fNIRS research has led to significant improvements in quality by following good experimental practices and protocols for data acquisition, ensuring appropriate quality assessment and formulating criteria for reporting outcomes. However, as highlighted in this work, these efforts seem to be poorly coordinated and often inconsistent, with several aspects still necessitating a consensus among fNIRS researchers. Further research should help define standard operating procedures to enhance methodological quality, increase reliability and consistency in results reporting, assist researchers new to fNIRS and improve cohesion amongst different optical imaging laboratories.
### Table 1. Taxonomy of experimental factors influencing fNIRS experimentation.

<table>
<thead>
<tr>
<th>Class</th>
<th>Family</th>
<th>Genera</th>
<th>Evidence based best practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Environmental</td>
<td>Ambient light</td>
<td>Room dimming, optode cover</td>
<td>• Dim laboratory lights.[a](#) • Shield and cover optodes.</td>
</tr>
<tr>
<td></td>
<td>Noise level</td>
<td>See attention</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Laboratory conditions</td>
<td>Temperature, humidity and ventilation</td>
<td>• Carry experiments at room temperature. [a](#) • Avoid extreme conditions.</td>
</tr>
<tr>
<td>Instrumentation</td>
<td>Illumination system</td>
<td>Laser heating time, cross-talk/wavelength selection, system drift (optode calibration)</td>
<td>• Warm-up lasers at least 30 mins. prior to data collection. • Utilize one wavelength at 830nm and a one between 660 and 770nm.</td>
</tr>
<tr>
<td></td>
<td>Propagating Fibres</td>
<td>Width, length, material and type of the optical fibres, stray-light rejection</td>
<td>• Glass fibres are more flexible, weigh less and provide improved measurements.</td>
</tr>
<tr>
<td></td>
<td>Laser safety</td>
<td>Laser power, tissue heating, injury to the skin, injury to the eye</td>
<td>• Laser power must be kept within IEC standard limits. • Always protect the eyes of the volunteers.</td>
</tr>
<tr>
<td></td>
<td>Detection system</td>
<td>Saturation, electromagnetic noise, emergent light dynamic range</td>
<td>• Data suffering from saturation artefacts must be identified and rejected from further analysis.</td>
</tr>
<tr>
<td>Mechanical</td>
<td>Interoptode distance</td>
<td>Depth sensitivity, Source-detector arrangement</td>
<td>• Typical interoptode distance is 30mm for adults and 20mm for infants.</td>
</tr>
<tr>
<td></td>
<td>Geometric optode</td>
<td>Optode arrangement, high density arrays, overlapping vs non-overlapping geometries</td>
<td>• High density multidistance and overlapping geometries can yield a better spatial resolution at the cost of higher reconstruction complexity.</td>
</tr>
<tr>
<td></td>
<td>configuration</td>
<td>Headgear and optode mounting devices, pressure, skin-optode coupling, optode movement</td>
<td>• Ensure adequate stable contact between the optodes and the scalp throughout the acquisition session. • Data contaminated by optode movement artefact must be identified.</td>
</tr>
<tr>
<td></td>
<td>Optode-Scalp coupling</td>
<td>Registration to standard systems, co-registration to fMRI systems, relocation, distance to targeted scalp location, probe size</td>
<td>• Registration to cortical surface is essential and efforts taken must be reported. • Location of optodes must be made against a standard positioning system.</td>
</tr>
<tr>
<td></td>
<td>Optode positioning, location and registration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td>Age, gender/sex, ethnicity/race, handedness, past medical history and current medical conditions</td>
<td>• Inclusion and exclusion criteria must be explicitly reported. • When appropriate, groups must be matched to minimize the effects of demographic confounders.</td>
<td></td>
</tr>
<tr>
<td>Population</td>
<td>Measurement day particulars</td>
<td>Stimulants intake (Caffeine, nicotine, alcohol, other drugs), and attention (noise level, cooperativeness and anticipatory response)</td>
<td>• Intake of stimulants by the cohort must be controlled for at least 24h. prior to data acquisition.</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Neurovascular-coupling</th>
<th>Spatiotemporal linear and nonlinearities and habituation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic</td>
<td>Heart rate/cardiac pulse, breathing and respiratory rate, arterial pulsation, blood pressure, cerebral circulation and gas exchange and scalp blood flux.</td>
</tr>
<tr>
<td>Extra-cranial</td>
<td>Scalp blood flux, scalp and skull thickness, hair</td>
</tr>
<tr>
<td>Intra-cranial</td>
<td>Dura mater, arachnoid, CSF and pia mater</td>
</tr>
</tbody>
</table>

- Interpretation of results must be made within understanding of the neurovascular coupling conditions.
- Physiological interference must be eliminated, reduced or incorporated as confounder during analysis.

| Protocol design | • Generic: Randomization, assumption checking, non-linear relations, indirect relations, control group/task, population size, |
|                | • fNIRS specific: paradigm (block vs event-related), number of trials, task length and intensity, rest periods/alternative task, and timings, temporal window for analysis and haemodynamic signal for analysis |
|                | • Pilot studies may help to adjust optimum experimentation parameters. |

| Image Reconstruction | Photon transport modelling, MBLL, differential pathlength factor, diffusion theory, temporal versus spatial reconstruction |
|                     | • Interpretation of results must be confined to the limits imposed by the assumptions made during the image reconstruction. |

| Image processing and analysis | Hypothesis based vs data-driven analysis framework, data integrity checks, software. |
|                              | • Data integrity checks must follow signal preprocessing. |
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