Unit 5 Lesson: A Very Brief Introduction to Neuroimaging

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Preface

This lesson intends to provide a brief introduction to some central neuroimaging methods that are relevant for studying the human brain. The lesson starts with a brief introduction to cognitive neuroscience as the basis of all cognitive processes, followed by a description of methods that can be used to measure brain responses. These are primarily two methods that will be presented here, which are (functional) magnetic resonance imaging (fMRI) and functional near-infrared spectroscopy (fNIRS). This overview can only touch on a few relevant topics and will be very selective in its examples and an in-depth study of these topics requires more than reading only this chapter. Each part of this chapter deserves a textbook on its own, and the reader is encouraged to continue reading from other sources, as well. Nevertheless, it is attempted to mention the most important aspects and developments briefly. However, the selection might appear to be weighted by personal interest and the overall topic of this book and should not be seen as a disregard of the not-mentioned work. The chapter ends with some reflections on the reliability and validity of the described methods.

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From Neurons to Networks

Neurons and Neurotransmitters

The human brain is the most developed and complex organ of the human body. It consists of around 90 billion neurons, which are those cells that are primarily involved in processing information, and about an equal number of nonneuronal cells (Herculano-Houzel, 2012). However, within the class of neurons, there is also specific differentiation into subcategories, specialised and optimised for the functions they need to perform. Although neurons can have many different shapes and functions, common to all neurons is that they have several extensions that split up into many further branches, which are dedicated to only receiving signals from other neurons. They are called *dendrites*. On the other hand, every neuron has only one single extension—that may later also split up into several branches—that is dedicated to only sending a signal to other neurons. This is called the *axon*. The third part of a neuron is the cell body, called the *soma* (Sidiropoulou et al., 2006). In summary, a neuron can have many dendrites for receiving signals, but it has only one axon for sending signals. However, due to the branching of both dendrites and the axon, each neuron can have contact with up to ten thousand other neurons.

The communication between neurons does not happen through direct contact between them—like with electric wires—but neurons form specific connection points called *synapses*, where neurons communicate through electrochemical processes. There, the axon of the sending neuron is separated from the dendrite of the receiving neuron only by the *synaptic cleft*, which is typically just a few nanometres wide. Here, the transmission of the signal from one neuron to the next happens through the release of *neurotransmitters*. Put very simply, the sending neuron releases the neurotransmitter into the synaptic cleft between the neurons, and the other neuron receives them. Suppose the released concentration of the neurotransmitter and the thereafter triggered neurochemical processes in the receiving neuron come over a certain threshold; in that case, the receiving neuron will generate an *action potential* through its axon to other neurons, aka "the neuron is firing". This is an "all or none" process, which means that once the triggering threshold is reached, the action potential will always be the same. However, it typically requires that the neuron receives time-synchronous signals from several neurons to trigger such a response. Note that each neuron of the brain is typically connected to thousands or ten thousand other neurons. The action potential itself is a neurochemical process based on a specific in and outflow of ions, like calcium, nitrogen, or chloride ions, which then generate a change in the electrical potential of the cell membrane, which propagates along the axon. This is a complex process that could only superficially be described here but might nonetheless illustrate the basic mechanism behind neuronal activations (Baslow, 2011; Shipp, 2007; Sidiropoulou et al., 2006).

Once the action potential arrives and the synapses, neurotransmitters are released. The most common neurotransmitters are *glutamate* and *dopamine*, which

are excitatory neurotransmitters, i.e. neurotransmitters that may cause the aforementioned process. By contrast, the neurotransmitter *GABA* is an inhibitory neurotransmitter that increases the threshold of an action potential and may therefore prohibit an action potential, even in the presence of other excitatory inputs from other neurons. Through this interplay of excitatory and inhibitory processes, the requirement of reaching certain thresholds in concentrations of neurotransmitters and other ions, and the dependency on the concentration of ions inside and outside of the neuronal cell, the brain can control the amount of simultaneously ongoing neuronal activation. On the other hand, it is also very vulnerable to disturbances which may cause this complex interdependent system to come out of balance. Several neurological and psychiatric disorders are caused by such a disturbance or unbalance of neurotransmitters (Falkenberg et al., 2014; Hugdahl et al., 2007; Hugdahl, Craven, et al., 2015; van Wageningen et al., 2009).

However, neurons are only one type of cell in the brain. There is an equal or even large amount of cells, called astrocytes, which perform a large number of functions that are essential for the brain to function. One of their functions is to recycle neurotransmitters after an action potential. Another essential function is to generate something that is called the *blood–brain-barrier*, which is essential for letting through only substances that are important for the neurons to function, such as oxygen or glucose while blocking others (Sweeney et al., 2019). Further, special types of astrocytes can form something around axons that is called *myelin*, which effectively increase the speed of action potentials or *glia* cells, which are important for the functional integrity of the brain (Stadelmann et al., 2019).

The Cortex

The brain has a hierarchical organisation with several substructures both on the macroscopic and microscopic scales. The vast majority of the already mentioned neurons are localised in a small strip along the outer surface of the brain. Therefore, this part of the brain is called the *cortex*, as it follows all the different folding of the brain, which are called *gyrus* (outward folding) and *sulcus* (the "valleys" of the cortex). The cortex itself typically has a substructure of 6 *layers*, which are subdivisions of the cortex, differing in the density and spatial distribution of neuronal cells, the type of neuronal cells, and their connectivity to neighboured or distant neurons. Further, these layers are differently organised and structured between different brain regions. This *cytoarchitectonic* segregation was first described by Korbinian Brodmann (Zilles & Amunts, 2010), who did pioneering work by identifying 43 cytoarchitectonic different brain areas in the human brain. There is a high degree of functional specificity between different cytoarchitectonic areas, which means that brain structures with a different cytoarchitectonic organisation also perform different functions. Therefore, it is still widespread that brain areas are not only described with their anatomical names but also in terms of *Brodmann area*, which follow more a functional differentiation. However, we now know that these

43 Brodmann areas need further subdivision and need to be treated differently for the left and right hemispheres.

Structural and Functional Brain Organisation

On the first glance, the brain consists of a few easily identifiable parts, which are the cerebrum (a), the cerebellum (b), and the brain stem. Further, these different parts look very symmetrical with a left and right half—called hemispheres—but they are not symmetrical, neither in their spatial configuration nor function. The cerebrum itself shows several clear landmarks. The most prominent one is the *medial longitudinal fissure*, which is the gap between the two hemispheres. The two hemispheres are connected through the *corpus callosum*, which is a big tract of mostly myelinated fibres that contains up to 250 million fibres connecting the two hemispheres.

Another prominent landmark is the *Sylvian fissure*, which defines the upper border of the *temporal lobe* and separates it from the *frontal and parietal lobes.* Functionally, the temporal lobe of the left and the right hemisphere are both mostly dedicated to the processing of acoustic stimuli, whereof the left temporal lobe is more dedicated to the processing of acoustically complex signals, such as speech. In contrast, the right temporal lobe is mainly dedicated to the processing of tonal signals, like prosody and characteristics of a voice, but also music (Sandmann et al., 2007; Specht, 2013, 2014). Accordingly, the left temporal lobe is the most important structure for speech perception since also central processes for the lexical, semantic, and syntactic deduction of spoken and written language information rely on various substructures of the temporal lobe (Specht, 2013, 2014). Interestingly, the left temporal lobe tends to be longer, while some of the folding of the right temporal lobe—in particular, the so-called *superior temporal sulcus*—tends to be deeper (Leroy et al., 2015; Specht & Wigglesworth, 2018).

The part of the brain behind the temporal lobe towards the back of the brain is dedicated to visual processing and is called the *occipital lobe.* The visual system is a complex hierarchical network of several modules that process different aspects of visually perceived information. For example, there are specialised modules within this network that perform actions like scene analysis, background-foreground separations, and global–local structures. In contrast, other modules differentiate between faces and objects, process the spatial localisation of an object, the colour of an object, or whether there are movements in the visual scene (Van Essen et al., 2001).

The part of the brain above the posterior end of the temporal lobe and superior to the occipital lobe is called the *parietal lobe.* Besides sensomotoric processing, this is a multifunctional brain structure which is involved in various higher cognitive processes. The parietal lobe is bordered by a landmark that is called the *central sulcus*, which separates the *frontal lobe* from the *parietal lobe.* While the sensory processing is posterior to the central sulcus in the parietal lobe, motor control processes are localised anterior to it, i.e. in the frontal lobe. The part of

the frontal lobe that is not dedicated to motor processing is called the *prefrontal cortex*. Compared to other species, the prefrontal cortex of the human brain is disproportionally larger. Functionally, the prefrontal cortex is mostly involved in higher cognitive processes, like cognitive control, inhibition of reflexive actions, short- and long-term action planning, social cognition, personality traits, working memory, focused and selective attention, and many more functions of our everyday life that require cognitive and executive control. Further, certain parts of the left frontal lobe are central to speech production processes (Brodal, 2016).

The structures that were mentioned so far, are only those that are visible from the outside. However, there are also important structures inside of the brain—the *subcortical structures*. Behind the Sylvian fissure is a part of the brain that is called the *insular cortex*, which is a multifunctional part of the brain, involved, among many other functions, in the reflexive direction of attention. Even deeper inside of the brain is the *basal ganglia*, which is composed of many substructures. The basal ganglia is very central in motor control processes but is also involved in various higher-order cognitive processes. The *hippocampus* is an important structure for memory formation, long-term memory, and spatial navigation, while the *amygdala* is a structure that is central for emotion processing and emotion regulation. Both structures, together with the *cingulate gyrus* are the core structures of the *limbic system*, which is considered to be central in long-term memory, emotion processing, and emotionally guided response behaviour (Brodal, 2016).

In the centre of the brain is the *thalamus*, which is the gateway for information to and from the brain. Almost all sensory signals—only the olfactory information has a different pathway—and all motor signals pass through the thalamus. Further, many structures and networks of the brain have reciprocal connections with the thalamus (Brodal, 2016).

Neuroimaging

Magnetic Resonance Imaging

This paragraph briefly introduces the complex physics behind magnetic resonance imaging (MRI). It was Paul C. Lauterbur who first introduced MRI in the early 1970, and the method rests on the already well-established method called *nuclear magnetic resonance* (NMR), which is mostly used in chemistry for analysing substances (Macovski, 2009; Wehrli, 2004). Put very simply, NMR and MRI make use of the magnetic properties and energy levels of atomic nuclei and their characteristic deviations in different chemical connections once it is exposed to a strong external magnetic field. In such an external magnetic field, the sub-elements of an atomic nucleus, namely the neutrons and protons, start to interact with the magnetic field. Their magnetic moments (*spin*) will rotate with an angular momentum and a specific rotation frequency (*Larmor frequency*) around the external magnetic field. This process mainly depends on the strength of the magnetic field and the chemical connection. By sending a radio wave with a certain frequency into

this system, the nuclei with the same rotation frequency will *resonate*. Thereby, it is possible to measure a spectrum of energy levels which in turn gives information about the presence of nuclei and their chemical connections in each probe. However, this is only a one-dimensional method. To create images, one needs spatial decoding, which was the essential development step from NMR to MRI (Macovski, 2009; Wehrli, 2004).

Paul C. Lauterbur was able to locally manipulate the strength of the magnetic field and hence generate spatial variations of the resonance signal. This can be achieved by applying *magnetic gradients* in addition to the main magnetic field, whereby "gradients" mean that the strength of the magnetic field increases along an axis. By doing so in all three dimensions, MR images can be generated. Further, MRI takes advantage of the fact that hydrogen atoms, which consist only of a single proton, are overwhelmingly present in the body since the human body consists almost exclusively of water and organic chemical connections, which contain hydrogen atoms.

An MRI scanner consists of three main parts: First, the main magnet, which creates a strong magnetic field of typically 1.5 or 3 Tesla, which is 30,000 to 60,000 times stronger than the earth's magnetic field. Seen from the outside, this is the dominating part of an MRI scanner, with an open tunnel in the middle that goes through the magnetic, and where the subjects are positioned for the examination since the magnetic field is most homogeneous in the middle of the tunnel. Such a strong and homogenous magnetic field is needed to let the spins of the hydrogen atoms (i.e. the single proton) rotate along the magnetic field lines with approximately the same Larmor frequency. The second main component is the gradient coils, which are inside of the magnetic. These gradient coils can slightly manipulate the strength of the magnetic field in all three dimensions. Thereby, the rotation frequencies (and phases) of the protons vary slightly at different places along the gradients. Third, the receiving coil (i.e. an antenna) will receive the signal that is transmitted by the spins in resonance after a radio wave is sent. In neuroimaging applications, this receiving coil is a *head coil* that is optimised to pick up the signal that comes from the head and which is typically placed around the subject's head.

Under an MRI examination, radio waves are repeatedly sent, and the strength and direction of the gradients are constantly changed. Those who already underwent an MRI examination will have noticed the noise such an MRI scanner generates—this is caused by the rapid switching of the gradients, which can generate substantial vibrations in the scanner. What happens under this process is that the spins of the hydrogen atom will respond to the radio wave (*excitation pulse*) by changing their rotation axis, for example, by flipping their axis by 90 degrees. After the radio wave has been switched off, the spins will return to their original rotation axis. Importantly, this process takes time, which is different for different tissue types. This time is called the *T1 relaxation*. For example, spins that are in grey matter, which is that part of the brain where all the neurons are localised, will need more time than spins that are in white matter, where all the long fibre connections run through. The combined information of these different T1 relaxation

times and the different strength and polarities of gradients will finally form a data space (*K space*) that is formed by frequency and phase information. From there, two and three-dimensional images can be reconstructed using, in the simplest case, a procedure that is called Fourier transformation (Macovski, 2009).

Similarly, after an excitation pulse, the spins are focused and aligned within a plane but get gradually out of phase. This process is tissue-dependent as well and is called *T2 relaxation.* However, this latter process is easily affected by local deviations of the magnetic field, which could be caused by, e.g. bones or air-filled caves. In this case, the T2 time is also affected and is then called the *T2* relaxation.* We will return to this in connection with functional examinations of brain activations.

The BOLD Signal

Both functional magnetic resonance (fMRI) and functional near-infrared spectroscopy (fNIRS) rest on the *BOLD effect* (BOLD = blood oxygenation level dependent). The BOLD effect has a metabolic origin and reflects neuronal activation only very indirectly. It makes use of the fact that haemoglobin is not only the main component of the blood but also the carrier of oxygen, which means it exists in two forms, namely as oxygenated, carrying oxygen atoms, and deoxygenated haemoglobin, without oxygen atoms. In the case of neuronal activation, the regional cerebral blood flow increases, and thus much more oxygenated blood floats into that area. However, since the oxygen extraction rate does not increase to the same degree, the relative concentration of oxygenated blood, which leaves the activated brain area, also increases. Since all MRI methods are based on differentiations of magnetic properties, this relative increase in oxygenation can be detected because oxygenated haemoglobin is diamagnetic and deoxygenated haemoglobin is paramagnetic (Kwong, 2012; Ogawa, 2012; Turner, 2012). This is the basis of most fMRI applications. Interestingly, oxygenated haemoglobin and deoxygenated haemoglobin also absorb infrared light differently, which forms the basis for fNIRS, as will be discussed later. However, it is important to emphasise that the BOLD signal is only a relative signal, which means that only a change in oxygenation level can be detected. This implies some limitations in how fMRI and fNIRS can be applied. It is essential that the experimental condition provokes a change in the oxygenation level. Otherwise, no signal will be measured. This is even true for the so-called *resting-state fMRI*.

The metabolic origin of the BOLD signal is also the reason why the signal is very smooth and stretched over time, which also implies that it does not reflect the neuronal activation per se. The BOLD signal is only a very indirect measure of brain activations—one could call it also a metabolic echo of brain actions. This must be remembered when interpreting fMRI and fNIRS data. While the temporal dynamics of neuronal activation is in the range of milliseconds, the corresponding BOLD signal is in the range of several seconds, with the strongest increase in the signal amplitude 4–6 seconds after the neuronal activation has happened. In other

words, the activation of the neurons might already have gone while the BOLD signal is still increasing. After the signal reaches its maximum, the signal decays over a period of 15–20 seconds, including a prominent post-stimulus undershoot, i.e. a signal drop below the baseline, before it reaches the baseline again.

The reason for this long-lasting and smooth BOLD signal and the post-stimulus undershoot can be explained by two mechanisms that are assumed to run in parallel. During and after neuronal activation, the inflow of deoxygenated blood from the capillaries into the veins is larger than its outflow, which causes an expansion of the veins. The prominent undershoot in the BOLD signal may result from a delayed cerebral blood volume recovery, i.e. widening and shrinking of the veins (Balloon model) (Richard B. Buxton, 2012; Buxton et al., 1998). The second mechanism is that the metabolism and the oxygen extraction are still increased while the regional blood flow has already decreased. This would increase the ratio of deoxygenated blood, which again would be reflected in a BOLD that drops below the baseline. A study by Hua and co-workers (Hua et al., 2011) using biophysical models comes to the conclusion that the observed BOLD signal behaviour is an intermix of these two different mechanisms, with a ratio of around 20:78, which has also been incorporated in the revised Balloon model (Buxton, 2012).

However, one general problem in this respect is the huge inter- but also intra-individual variability of the BOLD signal, which is partly caused by the metabolic origin but also by a low signal-to-noise ratio in the way the signal is measured. Therefore, an important limitation of all fMRI and fNIRS applications is that conclusions on the strength of activations, which means the amplitude of the BOLD signal, can only be drawn from group studies. Single-subject studies are only usable for localising some central functions, but any conclusions on activations strength are invalid. Therefore, fMRI hasn't yet shown a breakthrough as a diagnostic tool. In a clinical context, it is primarily used for presurgical mapping, where localising functions in relation to a tumour is of importance, not the activation strength (Specht, 2020).

Functional Magnetic Resonance Imaging

There are multiple ways of running MRI imaging protocols (often called *sequences*). While the physical principles are always the same, the different sequences can highlight different properties of the examined tissue; among them are the already introduced T1, T2, and T2* properties. In contrast to X-ray, which only can generate an X-ray image where the image reflects how much of the radiation came through the examined body part, MRI is a technique that can allow the generation of an increasing number of different types of images, where these images are able to highlight different (tissue) properties of the examined body part. Furthermore, this can be done within one examination, which makes it a very flexible tool with constantly growing new applications. One of these applications is functional magnetic resonance imaging (fMRI), which should be discussed in more detail.

Functional magnetic resonance imaging was invented at the end of 80th of the last century (Kwong, 2012; Ogawa, 2012; Turner, 2012) and makes use of the aforementioned BOLD effect. As described above, changes in the ratio of oxygenation of haemoglobin cause changes in the local magnetic environment around an activated brain area. As a result, more oxygenated blood creates a slightly more homogenous magnetic field in that activated area, which in turn causes a slight increase in voxel intensity. However, this only becomes detectable if the brain is scanned with a MR sequence that is sensitive to changes in magnetic environments. One such a sequence is a T2* weighted gradient-echo echo-planar-imaging (EPI) sequence, which is still the dominating way of detecting the BOLD signal (Bandettini et al., 1992, 1993, 1994; Brüning et al., 1995; Kwong, 2012; Turner, 2012). In short, the advantage of EPI is that it allows acquiring an entire slice with only one excitation pulse, thus acquiring the entire slice just in a fraction of a second (50–100 ms or less). Accordingly, the entire brain can be scanned within 2–3 seconds or, when applying multiband acquisition, even faster. However, EPI sequences are not only sensitive to the changes due to the BOLD effect but also to other so-called susceptibility artefacts, which are disturbances in the homogeneity of the magnetic field. Therefore, fMRI raw data are typically distorted. Some areas are whipped out by such artefacts, which appear, for example, at borders of air-filled cavities, like around the ear channels or above the nasal cavities.

Taking a historical perspective, the first decade of fMRI was predominantly marked by developments of the methods and investigations of the neuronal and physiological mechanisms behind the BOLD effect. This was, in particular, dominated by discussions on optimal experimental setups, like block- or event-related designs (see the next paragraph), design efficiency (Dale, 1999; Wager & Nichols, 2003), or adequate MR parameters. The second decade, by contrast, was more characterised by the application of fMRI for studying brain functions in healthy subjects and groups of patients. During that decade, the methods became more mature and more advanced and, more importantly, became broadly available. Accordingly, fMRI is no longer just used for brain mapping of single functions, but to an extended degree for creating multifunctional and hierarchical network models, for investigating dynamic and causal effects. The most prominent methods are the dynamic causal modelling (DCM) (Friston et al., 2019), independent component analysis (ICA) (Allen et al., 2014; Beckmann & Smith, 2004; Calhoun et al., 2004, 2012), multivariate pattern analysis (MVPA) (Hanke et al., 2009, 2010; Haxby, 2012), graph-theoretical approaches (Bullmore & Sporns, 2009; Sporns, 2018; Sporns et al., 2000), and several other methods, which cannot be listed all. The third decade was predominantly dominated by a new application of fMRI, called *resting-state fMRI (rs-fMRI)*, which will be described further down.

However, it should also be mentioned that even 30 years after its invention, fMRI has not found its way into broad clinical applications (Specht, 2020). The main reason is that fMRI is only an indirect measure of neuronal activations and could be described as a “metabolic echo” of neuronal activation. Further, the signal-to-noise ratio of the underlying BOLD signal is low, which makes it to a very unreliable signal. Accordingly, the magnitude of the BOLD signal has very

low reliability and could be easily influenced by many secondary factors. Therefore, fMRI is only clinically used for presurgical planning, where the localisation of a function is essential but not the amplitude of the underlying BOLD signal. The latter would be relevant for any further diagnostic purposes in, for example, neurology of psychiatry. This, however, works only when comparing larger groups of subjects (O'Connor & Zeffiro, 2019; Specht, 2020).

Task-Related fMRI

The described characteristic dynamic of the BOLD signal creates some limitations to the experimental design. On a 3T MRI, which is nowadays the most common field-strength for fMRI studies, the detectable signal changes are in the magnitude of not more than 3 or 4%, but increases when the study is conducted, for example, on a 7T MRI. In combination with the very fast EPI imaging technique, which has its own technical challenges, which cannot be discussed here, this results in a very low signal-to-noise ratio. Therefore, one needs both many repetitions of the tasks that should be examined and several subjects in order to generate reliable statistical results.

The most common and easiest way of performing an fMRI study is to use an experimental design that is called *block design* (Soares et al., 2016). Here, trains of stimuli belonging to the same condition are repeatedly presented over a period of ideally 15–30 seconds (*Task block*), alternated with blocks of control stimuli (*High-level baseline*) and/or equally long resting periods (*Low-level baseline* or *Off block*). These different blocks are then uninterruptedly and ideally repeated in random order at least 4 to 6 times per block and condition. Ideally, a study should contain both the high-level and the low-level baseline. This is the most efficient way to run an fMRI study as it generates the highest possible BOLD signal. Due to the nature of the BOLD effects, which has a total duration of up to 20–30 seconds after each trial, the BOLD signals to each trial within a block add up to each other, generating an overall high and stable BOLD signal. Such a design is especially recommended for studies of cognitive functions, where a weak signal might be expectable. From here, one could advance the experimental design to more complex setups with more conditions or parametric manipulations. However, there is one rule that applies to all types of experimental designs, which is that one needs several repetitions of the same condition.

A more flexible way of performing a task-related fMRI is to use a design that is called an *event-related design.* Here, only single trials are presented, followed by a brief rest period of typically 0.5–8 s before the subsequent trial is presented (Soares et al., 2016). This following trial might belong to the same experimental condition or to a different condition. Thereby, one can create experimental designs that are like those known from event-related potential (ERP) studies. However, one needs several repetitions (e.g. 30–40) for each trial per condition. In addition, the interval between trials should be randomly varied (*jitter*) between 0.5 and to several seconds, causing those types of studies to be often lengthy and tiering

for the participants, and the amplitude of the BOLD signal is much lower than for the block design. Therefore, one should be careful in selecting such a design for a study, although it allows more flexibility in some circumstances. Further, it requires exact timing and synchronisation between stimulus presentation and MRI image acquisition.

In general, it is mandatory to have control over the experimental timing for both block and event-related designs since the typical analysis of task fMRI is based on the experimental time course. Put very simply, a standard analysis of fMRI data is done through the specification of a general-linear model. In this model, a hypothetic BOLD signal is specified based on the timing of the tasks, which then generates an idealised hypothesis of when neurons are expected to be active and when at rest. This convolved with a prototypical course of the BOLD signal to form a set of regressors that are then fitted to the data. Therefore, it is essential always to have control over the timing of the tasks, as this fitting procedure would fail to find any relation between the task and the measured BOLD signal.

Resting State fMRI

In recent years, resting-state fMRI (rs-fMRI) has become a popular way of conducting fMRI studies. In contrast to task-related fMRI, where participants are asked to perform an experimental and a control task, the resting-state fMRI does not include any task. In the beginning, various forms of instructions have been used, like "*Close your eyes and don't fall asleep*", "*Keep your eyes open*", or "*Eyes open and fixate on the fixation cross*" (Raimondo et al., 2021), but also movie-watching has been used (Finn & Bandettini, 2021). Apparently, both fixation-cross and movie-watching give more reliable results than the "eyes closed" condition. The other still discussed question is for how long a resting-state fMRI acquisition should last. It has been shown that resting-state results are most reliable for scan durations of 9–13 min (Birn et al., 2013). Besides these considerations, the data acquisition is the same as for any other fMRI study. As described above, it is a prerequisite that a BOLD signal emerges, which means that the ratio of oxygenated to deoxygenated haemoglobin changes. This may sound paradoxical in the first place, given the fact that no instructions are given, and hence no hypothesis about the course of the BOLD signal can be generated. However, also rs-fMRI is based on measuring changes in the ratio of oxygenated to deoxygenated haemoglobin, but it rests on spontaneous low-frequent (<0.1 Hz) endogenous fluctuations of this ratio (Lee et al., 2013). It has been shown that these spontaneous fluctuations are not random but show characteristic spatiotemporal patterns, which mirror known functional networks, that are known from task-related fMRI, like the networks for executive functions, working memory, or visual as well as auditory perception (Smith et al., 2009). Each of these networks is characterised by a correlation of the BOLD signal, even if the different nodes of the network are distributed across the brain. Since a correlated BOLD signal is assumed to reflect coordinated activity, this indicates that these areas are functionally connected even in the absence of a

concrete task. Different methods have been developed and are still under development for analysing those fluctuations. One prominent method is the independent component analysis (ICA), which allows for identifying spatiotemporal patterns and separating them into a number of network components. An alternative for investigating rs-fMRI is a spectral DCM approach, where the spectral characteristic of these endogenous fluctuations within a given network of nodes is examined (Friston et al., 2014; Kandilarova et al., 2023; Razi et al., 2015).

One dominating network in the resting-state fMRI literature is the default-mode network (DMN), which is a network that primarily is activated during rest periods, and the interplay of the DMN network with its counterpart which is a network that is primarily active when the attention is focused to the outer world. Interestingly, this interplay is detectable in both resting-state and task-related fMRI (Hugdahl, Raichle, et al., 2015; Hugdahl, 2019; Kazimierczak et al., 2021; Raichle et al., 2001; Raichle & Snyder, 2007). Various studies have shown that the DMN and its dynamic shows deviating performance in neurological and psychiatric disorders such as schizophrenia or dementia (Kandilarova et al., 2023; Lee et al., 2013).

Functional Near-Infrared Spectroscopy (fNIRS)

An alternative technique to fMRI is *functional near-infrared spectroscopy (fNIRS)*. Although the method has been known for more than 40 years, it became increasingly popular only more recently through the development of wearable and wireless fNIRS devices (Pinti et al., 2018). The fNIRS method rests on the same metabolic principle as fMRI, i.e. the BOLD effect. However, it is much more flexible in its application and, therefore, potentially more relevant for future studies where fMRI might appear as not suitable. Like fMRI, the fNIRS signal originates from changes in the levels of oxygenated and deoxygenated haemoglobin in the brain. However, in contrast to fMRI, which rests on the different magnetic properties of oxygenated and deoxygenated haemoglobin, fNIRS is based on the physical effect that oxygenated and deoxygenated haemoglobin absorbs infrared light differently (Chen et al., 2020; Pinti et al., 2018). Hence, also fNIRS provides an equally indirect measure of neural activity as fMRI, and it is limited to only those brain regions that are closest to the skull. The method involves infrared light that is non-invasively transmitted through the skull to reach the cortex of the brain. This also includes that much infrared light is scattered, both at the level of the skull but also inside the cortex. However, the scattered light from inside the cortex forms the signal that is picked up by the fNIRS detectors. A fraction of the initially emitted infrared light reaches the cortex and is scattered back in a way that it reaches one of the detectors on the skull that are placed around the emitting infrared light source. Inside the cortex, oxygenated and deoxygenated haemoglobin absorbs infrared light differently and differently for different wavelengths. Therefore, most fNIRS systems operate with two wavelengths and, hence, measure different absorption spectra in depending on the amount of oxygenated and deoxygenated haemoglobin. A typical fNIRS system is assembled of a set of

infrared emitting *optodes* and infrared detecting *optodes*. In the case of neuronal activations, the ratio of oxygenated and deoxygenated haemoglobin will change, as described before, and the absorption spectrum in the infrared light that is scattered back to the detecting optodes on the skull will change. Thereby, and like fMRI, one can infer the potential brain activations somewhere between the infrared emitting and detecting optodes. This also describes one of the current disadvantages of fNIRS, which is its low spatial resolution, since the distance between the source and the detectors is in the range of 1–3 cm. On the other hand, this is to some extent outweighed by the advantage of being mobile and easy to apply in situations of social interactions (*hyperscanning* with 2 or more simultaneously examined subjects) and real-life conditions outside of the lab (Liu et al., 2022). Further, and in contrast to fMRI, fNIRS can infer on both the concentration of both oxygenated and deoxygenated haemoglobin.

Since they are based on the same metabolic origin, the overall time course of the fNIRS signal follows the same patterns as described for fMRI, and, accordingly, fNIRS has the same experimental limitations as fMRI, like that it requires enough repetitions per condition and several subjects per group.

However, fNIRS has several additional disadvantages that limit its use in certain situations. The limitation of the spatial resolution has already been mentioned, but, also the signal-to-noise ratio of fNIRS is lower compared to fMRI, which can make it difficult to detect small changes in brain activity. Although it is an advantage that some fNIRS systems are portable, they might be more affected by movement artefacts, but, some systems try to account for this by including gyroscopes to record head movements. However, despite these disadvantages, fNIRS has become a valuable tool for studying brain function and might become even more popular in the near future due to increased flexibility and increased performance, especially in open-field situations.

Variability and Reliability

In the previous chapters, a couple of limitations have already been mentioned. One of the most dominating limitations is the metabolic origin of the signals that fMRI and fNIRS measure. In the following chapter, it will be primarily focused on fMRI since more research has been done on this, and it is an ongoing discussion of how sensitive fMRI is and whether it is reliable enough for clinical applications. One must bear in mind that fMRI is based on physiological mechanisms where the ratio of oxygenated to deoxygenated blood must change. Otherwise, no BOLD signal will emerge, although neuronal activity might have occurred. This is of particular importance in clinical cases.

The BOLD signal is influenced by many parameters, like blood volume effects, the concentration of neurotransmitters, time of the day, blood pressure, body-mass index, the presence or absence of nicotine or caffeine, and many other factors (Honey & Bullmore, 2004; Sjuls & Specht, 2022; Specht, 2020; Specht et al., 2003; Vaisvilaite et al., 2022).

The dependency of fMRI on the occurrence of these metabolic effects is a dominating limitation. It has been shown that several factors can influence the BOLD signal. Those factors are, for example, blood pressure and body mass (Sjuls & Specht, 2022). Since blood pressure varies over the day, the time of the day has also been considered as a factor that might influence the BOLD signal (Vaisvilaite et al., 2022). Further, caffeine, nicotine and other pharmacological vasoactive substance affect the BOLD signal (Honey & Bullmore, 2004; Specht, 2020). Another source of inter-individual variability was discussed by Falkenberg and co-workers, who measured the concentration of the excitatory neurotransmitter glutamate in the anterior cingulate cortex (ACC), using MR spectroscopy (MRS). They detected that the subjects with high level of glutamate in the ACC showed a differential activation pattern during a cognitive control task than those with low glutamate, while the behavioural outcome was the same for these groups (Falkenberg et al., 2012). In the same vein, Muthukumaraswamy used MRS to measure the concentration of the inhibitory neurotransmitter GABA and found that this was negatively correlated with the BOLD-response amplitude but positively with the BOLD-response width (Muthukumaraswamy et al., 2009, 2012). This indicates that the BOLD signal is not a pure mechanistic response that is identical for each occasion but instead modulated by several other parameters, causing considerable inter-subject but also intra-subject variability. Therefore, several different methods for assessing the reliability of fMRI have been put forward, ranging from global measures, such as overlap estimates of activations across different occasions (Rombouts et al., 1998), receiver operating characteristics (Chen & Small, 2007), to variance-analytic measures, using, for example, the intra-class correlation coefficient (ICC) (Herting et al., 2018; Rødland et al., 2022; Specht et al., 2003), to name only some of the approaches. In general, the results demonstrate that attention-directed paradigms could achieve the highest reliability. In contrast, passive paradigms demonstrate less stable reliability, which is mainly discussed in the context of resting-state fMRI (Hjelmervik et al., 2014; Taxali et al., 2021).

Another source of the inter-subject variability is the anatomical between-subject variability, i.e. that even after a spatial normalisation of brain structures, functional areas are not overlapping and may also reflect individual brain-structural relationships (Genon et al., 2022). To illustrate individual variability, anatomical probability maps are good tool for showing those individual anatomical deviations, which may vary from one area to another. That this variability is also present in fMRI data and thus affecting group analyses data is nicely demonstrated by the comparison of fMRI-based probability maps and anatomical probability maps (Wilms et al., 2005; Wohlschläger et al., 2005). One approach for tackling individual variability is the use of navigator task, which are special fMRI tasks that aim to localise only one specific function, like visual motion perception within area V5/MT (Wilms et al., 2005).

Conclusion

In summary, both fMRI and fNIRS are neuroimaging methods that allow to examine the brain while processing stimuli, performing a experimentally controlled task, or even in a resting-state condition. However, both methods have their limitations. The most dominant limitation to both methods is the metabolic nature of the underlying BOLD signal, which is only a physiological consequence of a neuronal activation, which means, one doesn't measure a brain activation directly. This "metabolic echo" of a neuronal activation is both delayed in time and less precise in its location. Furthermore, a BOLD signal only emerges when there is change in the ratio of oxygenated to deoxygenated blood. If that doesn't emerge, both fMRI and fNIRS will not pick up any signal. This sets some limitations to the experimental design. If one is aware of all the inherent limitations of the described methods, neuroimaging is a valuable tool to study to human brain.

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