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MRI Techniques and New Animal Models for Imaging the Brain

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1. Introduction

This chapter describes how large animal models can be used to improve our knowledge of neuroscience and brain disorders. Various animal models have been used in Magnetic Resonance Imaging (MRI). Rodents and non-human primates are the most commonly used, but they present a number of drawbacks; for example, the rodent brain is smaller than that of humans and thus a higher spatial resolution is required. In addition, there are significant differences between human and rodent brain morphology: for example the rodent brain is smooth, whereas that of the human is gyrencephalic. By contrast, the brain of large mammals such as the pig, sheep or goat is gyrencephalic and has greater similarities with the human brain (Lind et al. 2007). The Göttingen minipig is increasingly used in experimental neuroscience, to investigate brain disorders and is a suitable alternative model to non-human primates for economic, ethical and genetical homogeneity reasons.

Functional imaging studies usually use the haemodynamic response to neuronal activity which induces the Blood Oxygenation Level Dependent (BOLD) effect. In general, BOLD functional MRI (fMRI) paradigms use block design protocols for stimulus presentation to study cognitive processes. However, due to a number of constraints (immobilization, conscious animals, etc.) these experimental paradigms are often unsuitable for animal models. The development of MRI apparatus for animals offers new MR imaging techniques to study brain functionality, including neuronal tracing by manganese-enhanced MRI, pharmacological MRI or MR Spectroscopy (MRS). Toxicity and acquisition time can make some of these techniques unsuitable for humans, and animal models could be used to overcome these problems and improve the signal-to-noise ratio.

The first part of this chapter describes MRI techniques that can be used as alternatives to typical block-design paradigms with large animal models, illustrated by a number of research examples. The second part explores the state of knowledge about the functioning of the central nervous system and its involvement in major functions and behaviour of farm animals such as the pig and sheep. We discuss the relevance of these animal models for human research into brain disorders.

2. MRI techniques

MRI is a non-invasive and *in vivo* technique, both essential features for biomedical research. It enables repeated measures to be carried out and also the longitudinal study of phenomena such as development, ageing, and the influence of environmental factors and physiopathology. MRI can also provide information about structural anatomy, functional activity, cerebral blood flow and water diffusion.

MRI uses a high magnetic field (B0) that aligns the magnetic spin of hydrogen atoms in the tissue in a low energy configuration. The spins are then excited out of equilibrium by a radiofrequency pulse. During the relaxation phase (return to equilibrium), time constants T1 (longitudinal magnetization) and T2 (transverse magnetization) can be measured. These values are used to construct MR images, as relaxation times differ across tissues.

One important advantage of MRI is its high spatial resolution associated with a higher grey/white matter contrast than in X-ray imaging. Due to these properties, cerebral structures can easily be identified. Depending on the animal model, the expected grey/white contrast, and the sequence of acquisition, it is possible to obtain an in-plane resolution of less than one millimetre and as low as tens of micrometres. Moreover, with its ability to perform rapid imaging (e.g. Echo Planar Imaging, EPI), MRI can also be used to obtain dynamic and thus functional imaging.

The most commonly used MRI techniques and their underlying principles are described below, illustrated by a number of studies.

2.1 Pratical issues, anaesthesia, and immobilization of animals

The brains of small ruminants and other mammals with a bodyweight of less than 150 kg (sheep, pigs, dogs, etc.) can be studied using conventional clinical scanners. Depending on the morphological specificities of the mammals involved (size, shape, presence of horns, etc.), surface or knee coils can be used.

The brain functions of healthy subjects can be studied using fMRI under non-invasive conditions and without injection of exogenous markers (e.g. radio-isotope). Recent advances have led to the possibility of imaging brain activity during cognitive processing, revealing the neural bases of various cognitive processes such as language (Vigneau et al. 2006), memory (Wager & Smith 2003), emotion (Sabatinelli et al. 2011), social cognition (Van Overwalle 2009) and neural network dysfunctions associated with various brain disorders (Ragland et al. 2007, Vocks et al. 2010). The method is based on localizing variations in blood flow or metabolism rates under basal or stimulated conditions. The method requires short-duration acquisition with repeated stimulations; the subject has to be immobile, which may require anaesthesia.

The question of anaesthesia has been raised for clinical applications with children (Orhan et al. 2011) and also for experimental applications, with large and small animals. The impact of various anaesthetics under different brain functioning conditions has been compared (for reviews: Boly et al. 2004, Gyulai 2004, Heinke & Schwarzbauer 2002), showing the importance of the type of anaesthetic (volatile e.g. halothane, isoflurane, or systemic e.g. propofol, ketamine), and the dose (low doses with analgesic effect without loss of consciousness, or higher doses with loss of ability to respond to commands). The impact of anaesthesia varies according to these factors and can be specific to a particular brain area (Fig. 1).

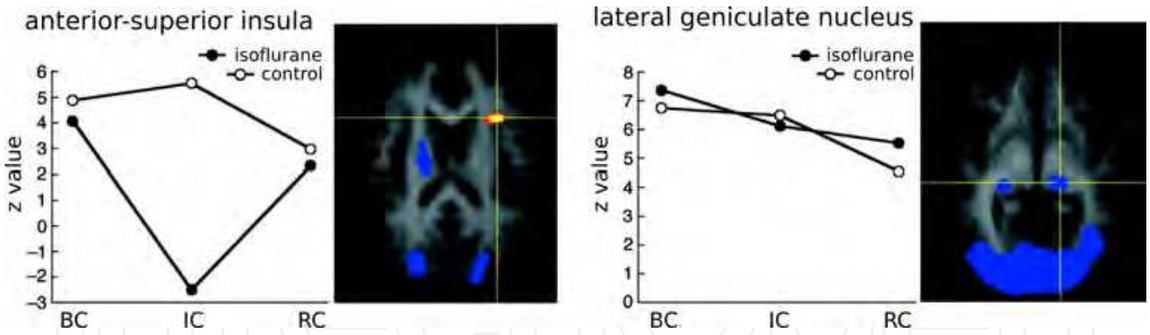

Fig. 1. Quantitative analysis of isoflurane-related changes in task-induced brain activation. Representative voxels were selected in two different regions (left: anterior-superior insula; right: lateral geniculate nucleus). The plots show the group-specific z-values for each group (isoflurane, control) and condition (BC=baseline condition; IC=isoflurane condition; RC=recovery condition). Comparing the corresponding time courses of the isoflurane and control groups reveals a significant isoflurane-related decrease ($z>3.1$ corresponding to $P<0.001$) in the anterior-superior insula, but not in the lateral geniculate nucleus. (Adapted from Heinke & Schwarzbauer 2002).

It is clear that the neural processes involved in cognitive functions cannot be studied under deep general anaesthesia; human brain activations induced by noxious, auditory or visual stimulations decrease in a dose-dependent manner after analgesia by ketamine (Rogers et al. 2004), and after sedation by propofol (Plourde et al. 2006, Purdon et al. 2009). In these studies, the authors described a decrease in BOLD in certain regions, but not in the primary cortical areas. Experimental studies with immobilized or anaesthetized animals have used new MRI paradigms with longer acquisition times or pharmacological agents, unsuitable for use with humans. For example, in a rat exposed to hypercapnia, brain activations were higher in conscious animals than those anaesthesia with isoflurane (Sicard et al. 2003). Conversely, the networks of vision, motor or auditory sensitivity described in the resting state persisted regardless of the depth or type of general anaesthesia (Hutchison et al. 2010), and no difference between anaesthetics was found after visual stimulation in dogs (Willis et al. 2001). Several MRI paradigms in anaesthetized animals have been developed to map brain activation induced by serotonin infusion in the baboon (Wey et al. 2010) and cat (Henderson et al. 2002) or brain connectivity in the rat (Pawela et al. 2009, Zhao et al. 2008).

Alternative functional MRI methods for paradigms requiring conscious animals, which comply with ethical standards of experimentation with large animal models, can be used to explore the organization and functioning of the brain (see section 3).

2.2 Structural studies

MRI allows brain images to be obtained with a very high spatial resolution (<0.5mm) and high grey/white matter contrast. Cortical and subortical structures can be easily segmented and their volumes can be determined precisely. Thus, both qualitative and quantitative studies can be conducted. T1-weighted images are mainly used for anatomical studies, but MRI can generate images based on numerous sequences and modalities, obtaining different contrast images (T2, T2*). Among T2-based sequences, Fluid Attenuated Inversion Recovery (FLAIR) enables an easier identification of white matter lesions by suppressing the signal from cerebro-spinal fluid (CSF).

2.2.1 Idenfication of structures – Qualitative studies

Schmidt and colleagues demonstrated that MRI is a useful tool for identifying and studying in detail anatomical cerebral structures in small ruminants (Fig. 2) (Schmidt et al. 2011). Using a conventional 1 Tesla MR scanner, they compared the brains of small ruminants with those of dogs and observed several distinct features (deep depression of the insula, pronounced gyri, larger diencephalon, and dominant positions of the visual and olfactory systems). Using a 4.7 Tesla MR scanner, Saikali and colleagues (Saikali et al. 2010) built a high-resolution (0.1x0.15x0.1mm) 3D atlas of the pig brain, including more than 100 cerebral and cerebellar regions. Although this atlas was constructed *post mortem* from one hemisphere, it can help to identify different structures.

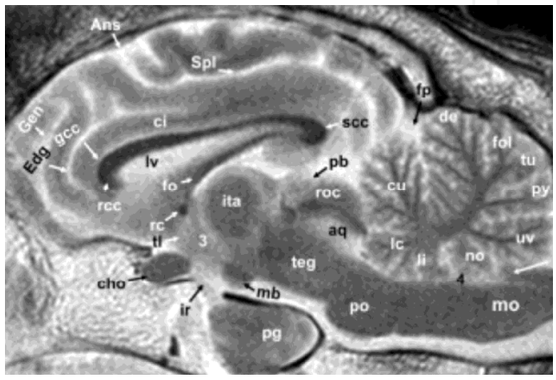

Fig. 2. T2-weighted mid-sagittal MRI of a sheep brain. (Adapted form Schmidt et al. 2011). Ans, ansate sulcus; aq, mesencephalic aqueduct; cho, optic chiasm; ci, cingulated gyrus; cu, culmen; de, declive; Edg, endogenual sulcus; fo, fornix; fol, folium; fp, primary fissure; fs, secondary fissure; gcc, genu of the corpus callosum; Gen, genual sulcus; ir, infundibular recess; ita, interthalamic adhesion; li, lingula; lc, central lobule; lv, lateral ventricle; mb, mamillary body; mo, medulla oblongata; no, nodulus; ob, obex; pb, pineal body; po, pons; py, pyramis; rc, rostral commissure; rcc, rostrum of the corpus callosum; roc, rostral colliculus; scc, splenium of the corpus callosum; Spl, splenial sulcus; teg, tegmentum of the mesencephalon; tu, tuber vermis; uv, uvula; 3, third ventricle; 4, fourth ventricle.

2.2.2 Morphometry – Quantitative studies

As mentioned above, MRI can be used for morphometric measures due to its high spatial resolution and grey/white matter contrast. Furthemore, as MRI is a non-invasive *in vivo* technique, it can be a valuable tool in longitudinal studies, revealing variations in the volume of cerebral structures. For example, it has been shown that an oestrogenic anabolic agent (zeranol) enhances the growth of the pituitary gland of rams (Carroll et al. 2007).

One limitation of morphometric studies is the anatomical variability between individuals. Most morphometric analysis methods in humans include a spatial normalisation step to overcome this problem. This involves a spatial transformation that places each individual brain in a standard, common space. This step requires a template of a standard target brain, which is constructed from several brains via linear affine coregistrations (see Collins et al. 1994 for method). Several templates (and atlases) have been constructed and are available,

but most of them concern non-human primates (Black et al. 2004, McLaren et al. 2009) and rodents (Schweinhardt et al. 2003). As mentioned above, a high-resolution atlas of the pig brain has been constructed (Saikali et al. 2010). The same researchers also built a 3D probabilistic pig brain atlas of the deep brain structures using *ex vivo* adult Large White pig brains. The DaNex study group has also computed a template of the average brain of the Göttingen minipig and a probabilistic atlas including 34 regions (Watanabe et al. 2001).

With the possibility of spatial normalisation, focal variations in brain anatomy can be studied by Voxel Based Morphometry (VBM). VBM is a statistical analysis method that consists in voxel-wise comparisons of the local concentration of grey (or white) matter. VBM includes various steps such as spatial normalisation and segmentation (white matter, grey matter and cerebro-spinal fluid). Voxel-wise statistical tests are then performed on these tissue maps to identify group-wise differences or longitudinal changes based on the General Linear Model (GLM) (Ashburner & Friston 2000). For example, a longitudinal paradigm has revealed that training induces grey/white matter volume changes in macaques (Quallo et al. 2009). VBM can also highlight phenotypic variations. It has been demonstrated that MRI, and particularly VBM, can be successfully used to test the heritability of cerebral anatomy in baboons (Rogers et al. 2007).

2.3 Magnetic Resonance Spectroscopy

Magnetic Resonance Spectroscopy (MRS) is widely used in both clinical and preclinical research for the *in vivo* study of cerebral metabolism and the quantification of numerous metabolites (Fig. 3). This quantification is computed from the MR spectrum (intensity of the resonance interaction against the frequency of the chemical compound). The frequency of each compound is linked to its chemical shift which is affected by the chemical environment of the hydrogen atoms. The area under the peak provides a measure of the relative abundance of the corresponding compound. Among the detectable peaks, creatine is used as a relative control value because its concentration remains relatively constant. For example, choline and lactate are considered as markers for brain tumours, while N-Acetylaspartate is used as a marker of neuronal integrity. The spectrum is usually acquired in one voxel (single voxel spectroscopy) and the size of this volume of interest (VOI) is around 1 cm^3. As acquisition time is not necessarily a constraint in animals, a smaller VOI size could be expected with a similar signal-to-noise ratio.

A limitation of MRS is that it uses metabolite ratios for quantification. This may produce ambiguous results whenever several metabolite levels vary simultaneously. An absolute quantification method has been developed (Barantin et al. 1997) called ERETIC (Electric REference To access In vivo Concentrations). It uses a synthetic reference signal which is synthesized as an amplitude modulated radio-frequency pulse, and is injected during the acquisition of the spectrum.

Due to their brain size, small animal brains require higher spatial resolution than for human brains to obtain similar acquisitions. In the macaque, MR spectroscopy has been performed successfully with a spatial resolution of 0.05 cm^3 (Gonen et al. 2008). These authors used multivoxel spectroscopy to compute 2D or 3D maps of spectra and to distinguish brain regions according to their metabolite content.

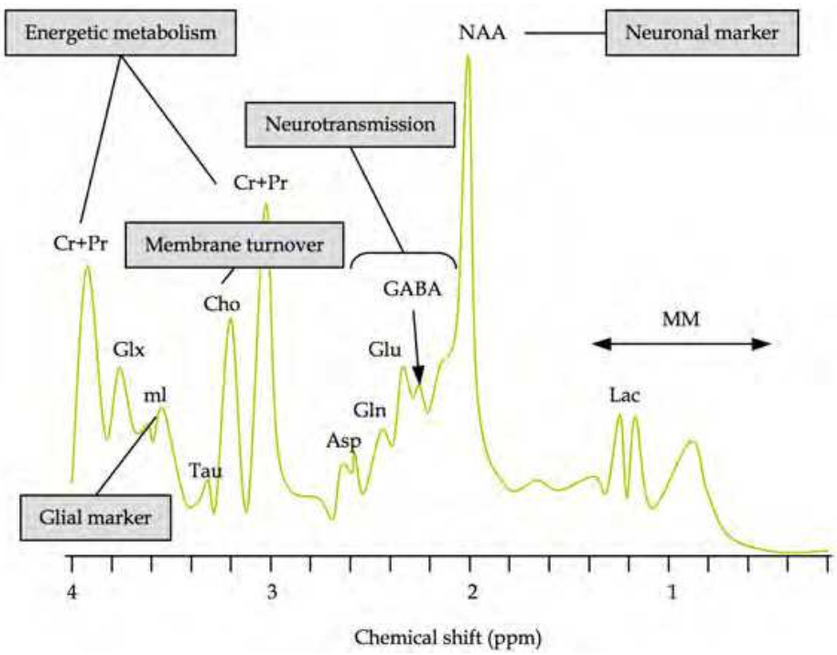

Fig. 3. Example of MR spectrum. Cr: Creatine, PCr: Phosphocreatine, Glx: Glutamate + Glutamine, ml: Myo-inositol, Tau: Taurine, Cho: Choline, Asp: Aspartate, Glu: Glutamate, Gln: Glutamine, NAA: N-Acetylaspartate, Lac: Lactate, MM: Macromolecules.

2.4 Contrast agents

The role of contrast agents is to improve the contrast-to-noise ratio and the spatial sensitivity of the MR signal. They are used in structural and functional studies. Several types of contrast agents have been proposed, some of them directly injected into blood vessels and others used to label cells that are subsequently injected. The use of several contrast agents is limited, especially in humans, due to their putative toxicity.

2.4.1 Gadolinium

Gadolinium (Gd) is a lanthanide metal with paramagnetic properties. However, as a free ion, Gd is highly toxic for mammals, so chelated Gd compounds are used as contrast agents. These agents enhance MRI by shortening the T1 relaxation time. In clinical examinations, Gd is widely used in MR angiography to enhance vessels. It is also commonly used for the exploration of brain tumours and blood-brain-barrier (BBB) integrity. Gd is a marker for BBB breakdown because it is restricted to the intravascular space when the BBB is not disrupted. Wuerfel and colleagues found that Gd-enhanced MRI could be successfully used to explore BBB changes *in-vivo* during the development of neuroinflammation (Wuerfel et al. 2010). A number of studies have also demonstrated the possibility of labelling and tracking cardio-vascular stem cells (Adler et al. 2009).

2.4.2 Manganese-Enchanced Magnetic Resonance Imaging (MEMRI)

Manganese ions (Mn^{2+}) are paramagnetic and enhance MRI contrast mainly by shortening the T1 relaxation time in tissue. Divalent Mn^{2+} is a calcium analogue and enters neurons

through voltage-gated Ca^{2+} channels. Due to these two properties, Mn^{2+} is a unique contrast agent for tracing axonal pathways and neuronal connections in the central nervous system (for review see Silva & Bock 2008). Injections of low concentrations of Mn^{2+} into a specific cerebral structure produce significant contrast enhancement along the known relative pathways (Watanabe et al. 2004). Jelsing and colleagues demonstrated in the Göttingen minipig that *in vivo* tracking with MEMRI is very sensitive and corresponds closely to histological labelling (Jelsing et al. 2006).

However, use of MEMRI remains limited because of the neurotoxicity of the Mn^{2+} ion at high concentrations (Shukakidze et al. 2003). Only one agent, Mn-dipyridoxyl-diphosphate, is used in human clinical imaging of the liver.

2.4.3 Inorganic nanoparticles

The main inorganic contrast agents in use are SuperParamagnetic Iron Oxide (SPIO) and Ultrasmall SuperParamagnetic Iron Oxide (USPIO) particles. They vary in size from 20-140nm for SPIO to 60-150nm for USPIO. When placed in a magnetic field, iron oxide particles induce local inhomogeneities, shortening T2 relaxation time. Iron oxide particles produce hypointensity on T2 and T2* weighted images and hyperintensity on T1-weighted images. The signal changes induced by iron oxide particles on T1 and T2 relaxation times are linked to the particle size and the compartment of the particles (extra/intracellular). The toxicity of nanoparticles seems to be limited, but their effect on stem cells is still discussed (Farrell et al. 2008, Muldoon et al. 2005, Schlorf et al. 2010).

Several works have also demonstrated that Monocrystalline Iron Oxide Nanocompounds (MION) can be used in functional studies in animals (Leite et al. 2002). Their main advantage is the specificity of fMRI signal change induced by MION which is only influenced by cerebral blood volume, whereas the BOLD signal is also influenced by cerebral blood flow (CBF) and the metabolic rate of oxygen.

An alternative way of using iron oxyde particles is cellular MRI. This technique allows to transplant and to follow labelled cells. Numerous studies have shown that *in vitro* neural stem and progenitor cells can be loaded with iron oxyde particles (for review Couillard-Despres & Aigner 2011). It has been suggested that this method has a very low detection threshold (Kustermann et al. 2008). One limitation of this method is that the detected contrast on MR images refers only to the particles and not to the labelled cells themselves. This could lead to non-specific observations due to the lack of information on type or viability of cells.

2.5 Diffusion Imaging and Diffusion Tensor Imaging

Diffusion MRI produces *in vivo* images of water diffusion (Le Bihan et al. 1986). Since water diffusion is affected by the microarchitecture of cerebral tissue, in particular the white matter, it can be used to study the organization of neural pathways. Measurement of diffusion provides a non-invasive imaging method to estimate cellular integrity and pathology, and to investigate disease-related changes in neuropathological processes that cannot be observed directly. Several measures can be computed, such as the average diffusivity, apparent diffusion coefficient (ADC), and the fraction of anisotropy (FA) that corresponds to the degree of anisotropy of the diffusion process. These variables are

influenced by factors such as fibre diameter or degree of myelination. Whole brain FA changes may be linked to numerous neuropathological mechanisms including neuronal loss, astrogliosis, myelin pallor and diffuse astrocytosis.

Diffusion tensor imaging (DTI) is an advanced method that produces images of the direction and the magnitude of water diffusion. DTI can be used to study white-matter fibre architecture and the influence of experience, disease or other factors on the white-matter fibre networks. Based on DTI data and the FA value of each voxel for several directions, different algorithms can be used to compute the location of white matter fibres and to perform tractography of the neural pathways. DTI can be considered as a functional imaging technique since it provides information about white matter tracts which carry functional information between brain regions.

2.6 Functional Magnetic Resonance Imaging (fMRI)

fMRI enables the measurement of BOLD changes associated with neuronal electrical activity. The BOLD effect is due to a local variation of desoxyhemoglobin concentration (acting as an endogenous contrast agent) which induces a T2* modification and a variation of the MR signal. fMRI uses EPI sequences that produces low spatial resolution images but with a relatively high sampling rate (typically 1–3 seconds). A time course of the MR signal (T2*) for each voxel can be computed. Neuronal activity induces a BOLD effect that affects the time course which is known as the haemodynamic response function. The relationship between neuronal activity and the BOLD effect is a combination of several physiological changes (cerebral blood flow, cerebral blood volumes, cerebral metabolic oxygen consumption, etc.) and is a subject of current research (Ekstrom 2010, Logothetis 2002).

When the effect of stimuli is assumed to be high, it can be examined by comparing the BOLD signal with and without stimulus presentation (Ferris et al. 2001, Makiranta et al. 2002). The size of the effect can then be estimated by computing the percentage of signal change ([average response over the stimulation period – average response over the control period]/[average response over the control period]) (Fig. 4). As the effect of the stimuli may be too weak to be observed with this method, block design paradigms have been developed.

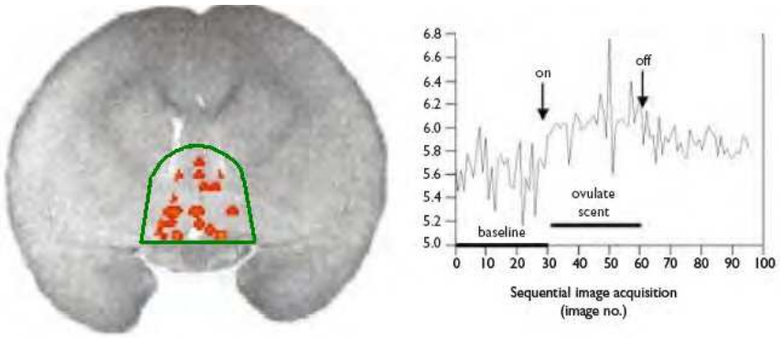

Fig. 4. Enhancement of BOLD signal in the preoptic area of male marmosets exposed to the scent of peri-ovulatory females. Red spots correspond to regions with a significant increase in the percentage of signal change during stimulus presentation. The average changes in signal in the region of interest (in green) are shown in the time course data. (Adapted from Ferris et al. 2001).

2.6.1 Typical activation studies: Block designs

Typical activation studies use block designs and analysis based on the general linear model (GLM). This method is used to make inferences about the effects of the stimuli by decomposing data into effects and errors, and computes statistical maps related to the effects of the stimuli (see Monti 2011 for principles). This kind of study is widely used in human and non-human primates, but due to a required subjects's involvement, typical fMRI activation paradigms have only been used in a few studies in large animals such as pigs or sheep (Fang et al. 2005b, Fang et al. 2005c, Fang et al. 2006, Opdam et al. 2002). Due to the constraints mentioned above (see 2.1), this kind of experimental paradigm will not be discussed further in this chapter.

2.6.2 Other experimental paradigms

The constraints relating to typical block activation paradigms can be avoided by analyzing the data with model-free methods. These do not require any presentation of stimuli and are thus also called data-driven analyses. One method widely used to identify brain networks is correlation analysis which is the most straightforward way to examine the functional connections of brain regions. It consists in computing correlations between the time course of the MR signal in one particular region (known as the seed region) against the time courses of all other regions, providing a connectivity map relative to the seed region. Numerous studies have used this method to explore the resting-state network in humans (van den Heuvel & Hulshoff Pol 2010 for review), non-human primates (Vincent et al. 2007) and rats (Zhang et al. 2010). One of the limitations of this method is that the functional connectivity map refers to a specific region and does not provide a whole-brain analysis.

Another data-driven approach is independent component analysis (ICA) whose goal is to recover independent sources given only observations. ICA transforms the observed signals into components and maximizes independency of these resulting components (see McKeown et al. 1998 for principles). In other words, ICA identifies functionally connected brain networks which covary independently of other regions. ICA has been used to explore resting state and functional connectivity in arousal states in humans, non-human primates (Moeller et al. 2009) and rodents (Hutchison et al. 2010).

2.6.3 Arterial Spin Labelling (ASL)

The ASL method measures CBF by providing cerebral perfusion maps without requiring a contrast agent. This approach uses magnetically labelled endogenous blood water as a freely diffusible tracer. The first studies were conducted in 1992 (Williams et al. 1992) and since then various improvements have been proposed. The principle of ASL is to sequencially acquire brain volumes and to obtain time series composed of tag images in which arterial blood is magnetically labelled (by apllying a 180 degre radiofrequency inversion pulse) and control images in which the inflowing blood is not labelled. First, the arterial blood water is tagged in a region that is proximal to the imaging region, and after a period of time the image of the region is acquired. The procedure is then repeated without the tagging step. This pattern of alternate acquisition is repeated several times. The difference between the control and tagged images provides a volume containing values proportional to the perfusion.

Because ASL measures CBF and uses rapid imaging sequences, activation studies similar to BOLD fMRI can be performed. The advantage of ASL-fMRI is that the ASL signal is thought

to be only associated with CBF in capillaries, while the BOLD effect results from numerous haemodynamic changes in nearby veins. However, ASL-fMRI has a lower signal-to-noise ratio, lower spatial and temporal resolutions, and can be less sensitive to stimuli.

In this section, we have described the different MRI techniques and their applications (Table 1). As there are a number of drawbacks to the use of rodents and non-human primates, commonly used in MRI investigations (see introduction), we propose the use of large animals (sheep, pigs) as alternative models. In the following section, we will outline the main advantages of using these models for a better understanding of cerebral functioning and related brain disorders.

		Resolution
MORPHOLOGY	**Structural Imaging**	<0.2mm^3
	Grey/white matter volumes	
	Long-term modifications	
	Diffusion Imaging	<10mm^3
	Architecture of white matter tracts	
	Long-term modifications	
FUNCTION	**Blood Oxygenation Level-Dependent Effect**	<5mm^3
	Neural bases of cognitive processes	
	Neural networks	
	Arterial Spin Labelling	<20mm^3
	Perfusion maps	
	Neural bases of cognitive processes	
METABOLISM	**MR Spectroscopy**	<1cm^3
	Metabolite distribution	
	Neuronal death	
	Neurogenesis	

Table 1. Summary of the main MRI applications.

3. Animal models

The central nervous system of farm animals has been studied to understand the regulation of major functions such as reproduction and food intake, with the aim of improving yields. Researchers soon found that these models could also be used to improve understanding of the brain (Lind et al. 2007, Sauleau et al. 2009) and the neurobiological regulation of various functions (Lehman et al. 2002, Malpaux et al. 2002, Skinner et al. 1997). The next section presents data obtained in large animals (pigs and sheep) providing fundamental knowledge about brain functioning and the central control of various functions and behaviours.

3.1 Brain injury

Large animals are commonly used as experimental models for human-infant research into brain disorders (pig, Lind et al. 2007), sudden infant death syndrome (pig, Tong et al. 1995), head injury (Lehman et al. 2002), brain injury induced by hypoxia (pig, Foster et al. 2001;

sheep, Laurini et al. 1999) or by preterm birth (sheep, Patural et al. 2010 , Pladys et al. 2008, Riddle et al. 2006), and neurobehavioural topics (pig, Friess et al. 2007). They can also be used for xenografts in Parkinson's disease (Molenaar et al. 1997). Some of these studies have focused on neuronal activation induced by hypercapnia in the dorsal vagal complex of piglets (Ruggiero et al. 1999, Sica et al. 1999) and on cyto-architectural modifications induced by hypoxia/ischaemia (HI), such as neuronal necrosis in the piglet hippocampus (Foster et al. 2001), while others have investigated cell degeneration in the cerebral cortex of fetal lambs (Riddle et al. 2006).

With regard to the development of MRI techniques, some authors have combined these approaches with histological methods. For example, Fang and collaborators studied the development of the pig brain (Fang et al. 2005a) and compared nociceptive and motor stimulations at different ages (Fang et al. 2005b). They demonstrated the usefulness of fMRI in non-anaesthetized piglets to identify differences in brain activation induced by pain stimulation and passive movement (Fang et al. 2005b). Immunohistochemistry enabled the authors to propose a hypothesis of functional brain maturation to explain the effect of age on brain activation measured by fMRI (Fang et al. 2005a). It has also been demonstrated that the volumetric analysis of brain lesions by MRI reveals the impact of traumatic brain injury in a similar way to histological approaches (Grate et al. 2003; Fig. 5). The use of MRI has been validated to detect HI injury in preterm fetal sheep, although detection was limited to injury in deep structures (Fraser et al. 2007). These studies demonstrate first how MRI and histology are complementary methods for understanding brain functioning, and secondly, that MRI produces similar results to histology while offering a more ethical approach.

Fig. 5. Serial T2-weighted MR images, histological section stained with hematoxylin and eosin, and adjacent section stained with an antibody against glial fibrillary acidic protein obtained at one-month post-injury in a one-month old piglet subjected to scaled focal brain injury. Note that the traumatic brain lesion (green arrow) is found whatever the method (adapted from Grate et al. 2003).

In the case of HI-induced brain injury in newborn piglets, magnetic resonance spectroscopy (MRS) has been used to monitor the cerebral metabolite ratio *in vivo* (Björkman et al. , Li et al. 2010, Vial et al. 2004). Björkman and colleagues measured the severity of the brain injury with EEG, ADC, MRS and neuropathological analysis. They observed correlations between these measures (Björkman et al. 2010).

MRI methods have also been used with large animal models in studies on epilepsy (sheep: Opdam et al. 2002), to develop new chemotherapeutic strategies such as local injection in the fourth ventricle (pig, Sandberg et al. 2008), and to test the toxicity of chemotherapeutic treatment on normal brain tissue close to the injection site (Makiranta et al. 2002). In sheep, MRI has validated *in vivo* ultra-sound transcranial brain surgery (Pernot et al. 2007).

3.2 Cerebrospinal fluid functionality

The ewe has commonly been used in neuroendocrinology studies as an animal model for neuroanatomical research (Lehman et al. 2002) into the neuroendocrine mechanisms of reproduction (Malpaux et al. 2002), or to study the effect of drugs on the central nervous system (Parry 1976). In this large animal model, CSF content can be analysed in real-time by continuous sampling over several days in conscious and unstressed animals at different stages of development (Dziegielewska et al. 1980, Tricoire et al. 2003).

Studies conducted in sheep have demonstrated that the gonadotropin releasing hormone (GnRH) pulses measured in the CSF are coincident with those measured in the hypophyseal portal blood and with the luteinizing hormone pulses measured in jugular blood (Skinner et al. 1997). Similar observations have been made for the melatonin (MLT) concentration measured in the jugular vein and CSF which vary with day-night rhythm (Skinner & Malpaux, 1999). It has been demonstrated in sheep that the CSF content varies according to the cerebroventricular compartment (Fig. 6, GnRH, Caraty & Skinner 2008; MLT, Malpaux et al. 2002, Tricoire et al. 2003), light-dark cycles (Skinner & Malpaux 1999, Thiery & Malpaux 2003, Thiery et al. 2003, Thiery et al. 2006, Thiery et al. 2009) and ageing (Chen et al. 2010a, Chen et al. 2010b). These findings suggest that the CSF is an active medium which could play a role in regulating various functions (Malpaux et al. 2002, Skipor & Thiery 2008).

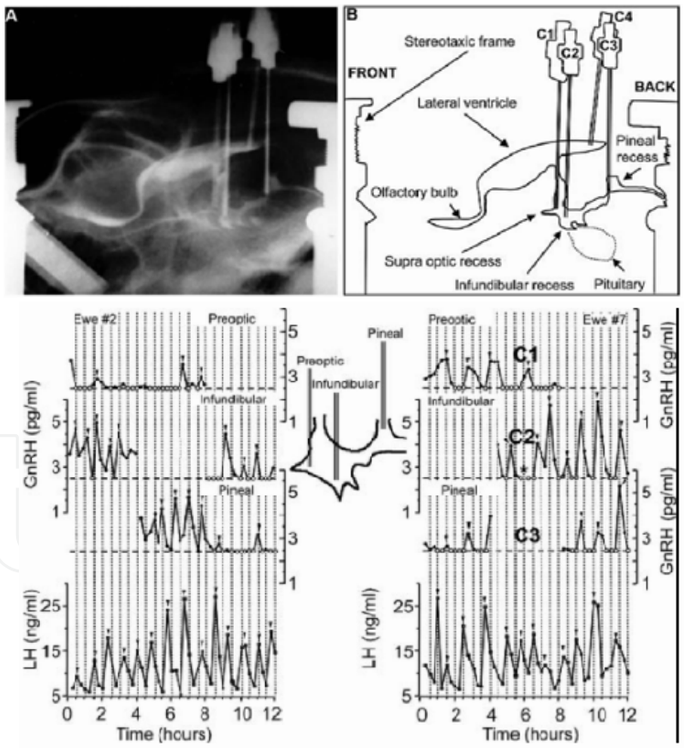

Fig. 6. A: Lateral X-ray image, and B: diagram showing the placement of the four cannulae implanted in the supraoptic (C1), infundibular (C2) and pineal (C3) recesses and in the lateral ventricle. C: Examples of GnRH concentration profiles in the CSF harvested simultaneously from the different cannulae (C1, C2, C3) with the corresponding LH secretion in the peripheral blood. (Adapted from Caraty & Skinner 2008).

One of the hypotheses regarding the variations in CSF content linked to season or ageing concerns variations in the BBB permeability, as demonstrated in sheep (Chen et al. 2010b, Lagaraine et al. 2011). BBB involvement and dysfunction in brain disorders has been extensively documented (de Vries et al. 1997, Forster 2008, Hawkins & Davis 2005, Strbian et al. 2008). Using MRI methods it is possible to study the BBB and its permeability in physiological or pathological paradigms (Hjort et al. 2008, Israeli et al. 2011, Wuerfel et al. 2010), and also to develop new therapeutic strategies (Liu et al. 2010).

Another hypothesis about the CSF-brain-endocrine interaction concerns tanycytes, which are ependymal cells of the third ventricle (Rodriguez et al. 2005). Their putative involvement in photoperiodic regulations has been described in the hamster (Ebling 2010). Apart from their physiological role, they are also implicated in brain disorders, as some chordoid gliomas could have a tanycytic origin (Sato et al. 2003). These tanycytoma are differentiated from other intracranial neoplasms by their specific location in the hypothalamus (Lieberman et al. 2003).

We therefore suggest that large animals such as pigs and sheep are relevant animal models, as the CSF content is easily measurable (e.g. in sheep), the permeability of the BBB can be investigated physiologically through day-night cycles (e.g. in sheep) and pharmacologically using ultrasound (e.g. in pigs, Xie et al. 2008).

3.3 Neurogenesis, cell proliferation

Evidence of adult neurogenesis was first presented in 1965 (Altman & Das 1965). It is now thought to play a role in different functions (Aimone et al. 2010) such as memory (Deng et al. 2010), in sensory systems such as olfaction (Whitman & Greer 2009), and in mental health disorders (Eisch et al. 2008), epilepsy (Rakhade & Jensen 2009) and Alzheimer's disease (Lazarov & Marr 2010).

In sheep, cell proliferation, evaluated by bromodeoxyuridine (BrdU) incorporation, has been observed in the dentate gyrus of the hippocampus of ewes exposed to a novel male (Hawken et al. 2009). Using BrdU incorporation and cellular biomarkers such as doublecortin or glial fibrillary acid protein (for review Sierra et al. 2011), it has been demonstrated that cell proliferation is down-regulated in the subventricular zone, the dentate gyrus and the main olfactory bulb at parturition and during interactions with the young (Brus et al. 2010, Fig. 7A). These authors suggest that cell proliferation could play a role in maternal behaviour via the olfactory and memory neuronal systems. New neurogenesis sites that could be involved in photoperiodic neuroendocrine systems have also been described in the hypothalamus (Migaud et al. 2010, Fig. 7B).

MRS is a promising method for visualizing and studying endogenous neural progenitor cells (Ramm et al. 2009, Sierra et al. 2011). *In vivo* imaging needs to be developed in humans (Couillard-Despres & Aigner 2011) to study adult neurogenesis (Couillard-Despres et al. 2011).

Based on current knowledge and available tools, we suggest that large animal models such as sheep can be used to validate the development of MRI techniques and to understand the role of neurogenesis through longitudinal *in vivo* studies.

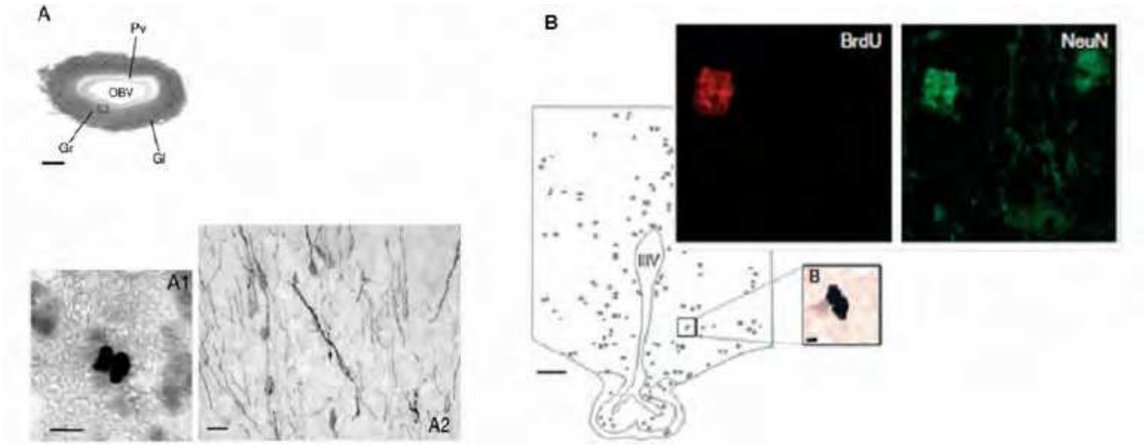

Fig. 7. BrdU integrated cells observed in the olfactory bulb (A, A1) and the hypothalamus (B) of adult sheep. In the main olfactory bulb, positive mature neuroblasts (A2) were observed in the same area as the BrdU incorporated cells (A1) at parturition (adapted from Brus et al., 2010). Constitutive cell proliferation observed in the adult sheep hypothalamus (B, BrdU in red), the new cells differentiated into mature neurons (NeuN in green) (adapted from Migaud et al. 2010).

3.4 Neurobiological regulation

3.4.1 Feeding behavior

The role of the central nervous system in regulating appetite and food intake has been extensively studied (for review Berthoud 2006, Kalra et al. 1999, Schwartz 2006). Regulatory systems in central areas include the hypothalamic system (ventromedian nucleus, arcuate nucleus, etc.), the caudal brainstem (area postrema, nucleus of the tractus solitary, etc.) and cortical structures (prefrontal cortex, amygdala, hippocampus, etc.). At the hypothalamic level, numerous neuropeptides have been identified as major orexigens (neuropeptide Y, galanin, etc.) or anorexigens (cholecystokinin, somatostatin, etc.), most of them regulated by hormones such as insulin or leptin. In sheep, similar factors have been observed to regulate food intake (Baile & McLaughlin 1987, Chaillou et al. 2000, Della-Fera & Baile 1984) or to be regulated by nutrition (Chaillou & Tillet 2005, Zieba et al. 2008). The same factors have been described in the pig (Baldwin et al. 1990a, Baldwin et al. 1990b, Baldwin & Sukhchai 1996, Czaja et al. 2002, Czaja et al. 2007, Parrott et al. 1986), and similarities have also been found in humans for preferences for sweet food (Houpt et al. 1979) and for energy metabolism (Spurlock & Gabler 2008). All these observations support the idea that the pig can be used as a model for human studies (Johansen et al. 2001).

Knowledge about the central regulation of feeding behaviour has been documented using techniques including central injections of neuropeptides or hormones, comparison of neuropeptide expression levels in different nutritional states, and more recently by MRI (Van Vugt 2010). MRI has been used in human studies of the cognitive component of eating disorders such as anorexia nervosa (volumetric MRI, Muhlau et al. 2007; fMRI, Vocks et al. 2010) or nutritional disorders such as obesity (fMRI, Killgore & Yurgelun-Todd 2010).

We suggest that large animal models could be used to study the putative consequences on human brain functioning of nutritional disorders such as obesity. For example, functional

connectivity, measured by MRI, is impaired in obese human subjects, and is correlated with metabolic indicators such as insulin (Kullmann et al. 2011). It would be interesting to compare the impact of different neuropeptides or diets on brain activation that could be measured at different times of life, but this type of protocol would be difficult to standardize in humans. The effects of gastric bypass surgery on hypothalamic functional connectivity and on various indicators (inflammatory and metabolic) have been studied in obese human subjects (van de Sande-Lee et al. 2011). Similar protocols could be designed in the pig, making it easier to select animals and to set up a sham-surgery control group, and could be used to study the long-term effects of surgery. Other studies could investigate interactions between nutrition and other functions such as reproduction, or to evaluate the putative sensorial effects induced by cognitive perturbations during prenatal, perinatal or childhood periods. For example, a recent brain imaging investigation using PET scan compared the cerebral blood flow of lean and obese minipigs (Val-Laillet et al. 2011).

3.4.2 Reproduction

Reproduction is controlled by the central nervous system, more particularly by the hypothalamus where the neuronal population containing GnRH is located. This neuropeptide is the key factor in the regulation of the hypothalamic- pituitary-gonadal axis. It is released in a pulsatile fashion into the hypophyseal portal blood. Numerous studies have been performed using a sheep model, as the oestrus cycle of ewes has the same temporal pattern as the menstrual cycle of women, and because it is possible to sample blood from the hypophyseal portal system of the ewe (Caraty et al. 1982). Many peripheral hormones from the gonads act on distinct neuronal populations in the brain to regulate the neuronal activity of GnRH neurons. The neuronal network controlling reproduction in sheep has been extensively described, and the neuroendocrine factors regulating this network are known (steroids, neuropeptides, monoamines, etc; for reviews Herbison 1995, Herbison 2006, Tillet 1995). All these data have contributed to our knowledge of the central control of reproduction in mammals, and more particularly in humans.

However, one outstanding difficulty concerns the precise description of the temporal activations and interactions between the different neuronal partners in regulating the menstrual cycle and puberty. MRI could help to overcome this difficulty and a number of studies have already been performed in humans to investigate the interaction between the neuronal population and the feedback effect of gonadal hormones. At puberty, when the gonads start to produce hormones and particularly steroids, MRI methods have been used to determine how steroids (oestrogen and testosterone) act on brain development and plasticity (Jernigan et al. 2011). Another field of study has focused on brain functioning in women during the menstrual cycle. Throughout the cycle, the ovaries produce successively increasing levels of oestradiol and progesterone (Goodman & Inskeep 2006), concomitant with changes in functional cerebral asymmetries (Weis & Hausmann 2010) which are potentially due to variations in functional connectivity (Weis et al. 2010). These hormonal variations during the menstrual cycle or caused by hormonal contraceptives affect the volumes of grey matter (Pletzer et al. 2010) and modify the activation induced by negative emotion in the amygdala and hippocampus as demonstrated by fMRI (Andreano & Cahill 2010), and hormonal variations also affect food perception in interaction with feeding disorders (Van Vugt 2010). These data have been obtained under clinical conditions and it is clearly impossible to extend these human studies for obvious ethical reasons. The female sheep is an excellent model to

understand the central effect of steroids on brain functioning and can also be very useful for developing treatment strategies for central or pituitary infertility in humans, and for investigating central effects of new therapeutics and contraceptives.

3.4.3 Social behaviour

For all species, the neuronal networks involved in social behaviour combine autonomic regulatory and sensorial integrative structures. In the case of sexual and maternal behaviour, partner recognition results from the interaction between the olfactory system (the main sense involved in social recognition), and the neuroendocrine circuit involved in oestrus for sexual behaviour and parturition for maternal behaviour (Gelez & Fabre-Nys 2006, Levy & Keller 2009, Poindron et al. 2007). Similarly, olfaction is important in establishing maternal recognition by the lamb, and the development of the mother-young bond is reinforced by oro-gastro-intestinal stimulation (Nowak et al. 2007). However, while olfaction is the first proximal sense used (i) by the mother and infant to establish a bond, and (ii) by the male and female to identify social partners, visual (Kendrick et al. 2001) and auditory (Sebe et al. 2007, Sebe et al. 2008) factors are also involved in the expression of social preferences.

In order to understand social behavioural, disorders, and the establishment of social bonds, we need to study the sensory systems and how they interact with the neuroendocrine system. Neuroanatomical approaches require a large sample and complex protocols. MRI techniques can be used to show how the brain discriminates social sensory indices or is activated by social neuroendocrine factors. For example, the BOLD signal of conscious non-human primate males exposed to the scent of peri-ovulatory females is greater than when exposed to the scent of ovariectomized females in various hypothalamic (Ferris et al. 2001; see above Fig. 4) and cortical areas (Ferris et al. 2004). With regard to the formation of a maternal bond in the rat, it has been shown that suckling activates similar brain areas to those activated by a central injection of oxytocin (Febo et al. 2005), a neuropeptide involved in social attachment (Young et al. 2008) and maternal behaviour (Levy et al. 2004).

Ungulates are similar to humans in the preference shown by the mother for her own offspring, a process known as maternal selectivity (Poindron et al. 2007). This suggests that ewes could provide an interesting model to investigate disorders of maternal behaviour. For example, the impact of the offspring's odour on variations in cerebral blood flow could be compared between selective, maternal, and non-maternal ewes. Functional connectivity MRI could also be used to describe the dynamic functional interactions between the cortical structures involved in sensory integration and deep structures such as the hypothalamus or amygdala, since the neuroanatomical connections between these neuronal systems are known in sheep (Levy et al. 1999, Meurisse et al. 2009).

3.4.4 Emotional reaction

Animals' emotional reactions can be described through behavioural and physiological responses. These are regulated in mammals by numerous neuronal networks: the corticotrope axis (Herman et al. 2003), the brainstem, and the periaqueductal grey matter that regulates motor responses (Keay & Bandler 2001, LeDoux 2000). These deep structures interact with the prefrontal cortex and the amygdala (Herman et al. 2003, Keay & Bandler 2001, LeDoux 2000) and are all involved with neurochemical factors as cortico-releasing factor (CRF), and serotoninergic and dopaminergic systems (Charney 2004, Rotzinger et al.

2010). In large animals, such as sheep or pigs, similar neurobiological factors have been found to be involved in emotional responses, especially in stressful situations. Invasive neurobiological approaches based on functional neuroanatomy (sheep: da Costa et al. 2004, Rivalland et al. 2007, Vellucci & Parrott 1994), intracerebroventricular pharmacology (pigs: Johnson et al. 1994, Salak-Johnson et al. 2004), and neurochemical brain content (e.g. in pigs, Kanitz et al. 2003, Loijens et al. 2002, Piekarzewska et al. 1999, Piekarzewska et al. 2000, Zanella et al. 1996) have demonstrated the involvement of neuropeptides such as CRF and enkephalins in different brain areas including the hypothalamus, brainstem and cortices. While neuroanatomical methods have been used to describe the immunoreactive content of brain areas (in sheep: Tillet 1995; in pigs: Kineman et al. 1989, Leshin et al. 1996, Niblock et al. 2005, Rowniak et al. 2008; in large mammals: Tillet & Kitahama, 1998), and neuronal-tracing methods have been used to describe the interconnections between some of these brain areas (sheep: Qi et al. 2008, Rivalland et al. 2006, Tillet et al. 1993, Tillet et al. 2000; pigs: Chaillou et al. 2009), no dynamic functional information is available about the functional interactions among these different factors. The use of MRI techniques could be an interesting way of gaining a better understanding of the neuronal circuits of animal emotion and other functions.

MRI has been used in humans to develop knowledge of the neuroscience of emotions (Junghofer et al. 2006), describing the neuronal circuit in order to demonstrate the impact of pathological emotional behaviour (e.g. posttraumatic stress disorder) on hippocampal volume (Wang et al. 2010) or the effects of antidepressants in major depression (Bellani et al. 2011). These studies have all focused on cortical structures. The posterior hypothalamic area has been shown to play a major role in seasonal affective disorder (SAD) (Vandewalle et al. 2011). The sheep has been proposed as a model for SAD as it is a photoperiodic mammal. More information is now available in sheep about emotional states (Guesdon et al. 2011) and how they can be modified (Doyle et al. 2011, Erhard et al. 2004, Greiveldinger et al. 2007, Vandenheede & Bouissou 1998). For example, it has been suggested that the serotoninergic pathway is involved in the affective state of sheep (Doyle et al. 2011). MRI techniques could be used to investigate the impact of various neurobiological factors on emotional state, as shown in pharmacological models of depression (Michael-Titus et al. 2008). More interestingly, we propose the use of large animal models to study the long-term effects of strong acute emotion in prenatal or perinatal life on brain development and behaviour. For example in the pig, prenatal stresses have been shown to affect ontogeny of the corticotrope axis (Kanitz et al. 2003) and behaviour (Jarvis et al. 2006).

We suggest that large animal models can be used to validate and/or study the impact of non-pharmacological clinical treatments that are now used in mood and anxiety disorders (Ressler & Mayberg 2007), using standardized protocols that are inappropriate to conduct in humans.

4. Conclusion

This chapter described various MRI methods and their use in exploring brain anatomy and functioning in large animal models. We discussed the way these models can be used to study brain injury such as hypoxia/ischaemia, and the different compartments of the central nervous system (e.g. CSF) or neurobiological control (e.g. food intake).

The brain circumvolutions, the brain size and development as well as the neurobiological regulations are the most evident arguments to justify the interest for large animal models for

human brain studies. These models also present many advantages for studying the dynamic functional interactions between brain structures using functional connectivity MRI, to understand the interaction between different brain functions with fMRI and for conducting standardized longitudinal studies that are not feasible in human studies. They can also be used to test new surgical procedures and the impact of treatment on healthy brain tissue and behaviour.

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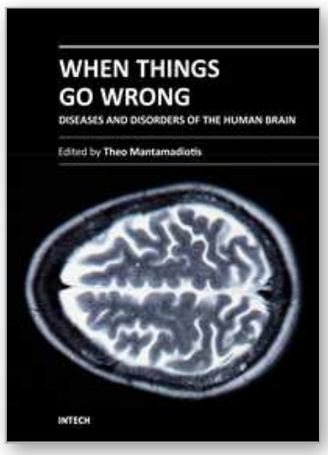

When Things Go Wrong - Diseases and Disorders of the Human Brain

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In this book we have experts writing on various neuroscience topics ranging from mental illness, syndromes, compulsive disorders, brain cancer and advances in therapies and imaging techniques. Although diverse, the topics provide an overview of an array of diseases and their underlying causes, as well as advances in the treatment of these ailments. This book includes three chapters dedicated to neurodegenerative diseases, undoubtedly a group of diseases of huge socio-economic importance due to the number of people currently suffering from this type of disease but also the prediction of a huge increase in the number of people becoming afflicted. The book also includes a chapter on the molecular and cellular aspects of brain cancer, a disease which is still amongst the least treatable of cancers.

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