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## The ovine motor cortex: A review of functional mapping and cytoarchitecture



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### ABSTRACT

In recent years, sheep (*Ovis aries*) have emerged as a useful animal model for neurological research due to their relatively large brain and blood vessel size, their cortical architecture, and their docile temperament. However, the functional anatomy of sheep brain is not as well studied as that of non-human primates, rodents, and felines. For example, while the location of the sheep motor cortex has been known for many years, there have been few studies of the somatotopy of the motor cortex and there were a range of discrepancies across them. The motivation for this review is to provide a definitive resource for studies of the sheep motor cortex. This work critically reviews the literature examining the organization of the motor cortex in sheep, utilizing studies that have applied direct electrical stimulation and histological methods. A clearer understanding of the sheep brain will facilitate and progress the use of this species as a scientific animal model for neurological research.

### 1. Introduction

Pioneering studies in the late 19th century to early 20th century (Fritsch and Hitzig, 1870; Penfield and Boldrey, 1937) showed that electrically stimulating the motor cortex generates muscle contraction. These early studies have led to one and a half centuries of research in brain mapping (Johnson et al., 2013; Tharin and Golby, 2007) that have aided in the treatment and management of central nervous system disorders (Brown, 2001; Tharin and Golby, 2007). The use of electrical stimulation to evaluate functional attributes of the brain, such as motor somatotopy, was critical in brain research and in identifying clinically appropriate animal models.

Non-human primate brains are anatomically and functionally similar to the human brain (Bontrop, 2001; Capitanio and Emborg, 2008). However, primates such as macaques have much smaller brains and blood vessels than humans, and marmosets show significant

anatomical differences to humans. In addition, the complexity and cost of using non-human primates may also add significant constraints. Small animals such as rodents, despite some similarities to the function and organization to the human brain (Byrom et al., 2010; Fletcher et al., 2011; Neill et al., 2010; Nestler and Hyman, 2010), are vastly different in size and anatomy to humans and have short life spans, making them less suitable. In fact, when developing therapies and devices for the brain or cortical blood vessels, large animal models such as sheep, cats, pigs, and dogs are necessary (Boltze et al., 2008; Byrom et al., 2010; Margalit et al., 2003; Morimoto et al., 2011; Oxley et al., 2016; Rooney and Cowan, 2011; Schanze et al., 2006; Schnabl et al., 2012; Shon et al., 2010; Silfverhuth et al., 2011).

*Ovis aries* (sheep) are a viable alternative large animal model for preclinical validation of neural implants, and studies have demonstrated that they may be used as suitable models for a range of conditions including epilepsy, psychiatric and neurological dysfunction, and

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sensory, vascular, cardiac, and renal dysfunction (Bertschinger et al., 2008; Byrom et al., 2010; Jardine et al., 2002; Nestler and Hyman, 2010; Ramchandra et al., 2013; Rogers et al., 2009; van der Staay, 2006). Sheep's cognitive abilities (Kendrick et al., 2001; Lee et al., 2006; Morton and Avanzo, 2011) have seen it being used as a Huntington's model and in preclinical studies of neural implants (Stypulkowski et al., 2013). Furthermore, craniotomy in sheep is easier than other animal models as the size of muscles (*m. frontalis*, *m. interscutularis* and *m. tempoerialis*) overlying the skull are smaller in sheep than in other large animal models, such as the dog. However, little use has been made of sheep for neurophysiological research compared with cats, mice, and non-human primates, in part due to a lack of understanding of the sheep brain. Further, functional mapping studies in sheep are necessary to better understand the sheep brain and nervous system.

This review was motivated by the lack of a definitive resource that describes the sheep brain and motor cortex. Here, we critically review the literature describing the location, cytoarchitecture, and somatotopic function of the motor cortex in sheep. We discuss findings from both cytoarchitecture and functional mapping to elucidate comparability to other animal models and humans, as well as the applicability of sheep as an animal model. We hope this review will enable researchers to make informed decisions when considering using sheep as a model for translational research of motor function/dysfunction.

## 2. Literature survey

We performed a search on PubMed with the keyword search terms “sheep” or “ovine” and “motor cortex”. In addition; a further search was performed based on references found in these journal articles. Articles in languages other than English were translated internally and the results are discussed.

### 2.1. The sheep motor cortex

The sheep brain is analogous to the human brain in many respects and can be similarly divided into four lobes: frontal, parietal, temporal, and occipital lobes (Kendrick et al., 2001). Fig. 1 shows the major sulci and gyri in the sheep cortex (Landacre, 1930). However, several differences from the human brain can be seen in the anatomical organization of the sheep brain. The frontal lobe lies anterior to the ansate (cruciate) sulcus, extending medially from the interhemispheric fissure and the diagonal sulcus and on the lateral aspect of the brain. There are a few indications that higher cognitive function, such as decision making, occurs in the parietal or temporal lobes (Kendrick et al., 2001). In sheep, the motor cortex (Dinopoulos et al., 1985) and somatosensory cortex (Johnson et al., 1974) lie in the frontal lobes running parallel to the interhemispheric fissure. However, in humans, the motor cortex lies in the frontal lobe while the somatosensory cortex lies in the parietal lobe and are divided by the central sulcus (Standing, 2015). Currently, the sheep motor cortex has not been subdivided into pre-motor or supplemental motor cortices. In the following sections, we review the functional mapping literature relating to the motor and somatosensory areas, followed by a review of the anatomical profile of the sheep brain focusing on the pyramidal neurons of the motor areas.

### 2.2. Functional mapping of the sheep motor cortex

Direct cortical electrical stimulation is commonly used to identify functional areas of the motor cortex and is considered the gold standard for functional mapping due to the generally causal relationship between the stimulation and response (Brown, 2001; Donoghue et al., 1992; Donoghue and Wise, 1982; Graziano et al., 2005; Hall and Lindholm, 1974; Phillips and Porter, 1962). Since 1877, numerous studies have used electrical stimulation to define the motor area in the sheep brain (Bagley, 1922; Bianchi, 1920; Dexler and Margulies, 1906; Grovum and

Gonzalez, 1999; Marcacci, 1877; Simpson and King, 1911; Ziehen, 1899). A schematic diagram of the various areas that generated overt motor responses in these studies are shown in Fig. 2, and a detailed outline and experimental parameters are provided in Table 1. The study by Dexler and Margulies (1906) did not yield any responses and so is not shown in Fig. 2.

#### 2.2.1. Functional location of the motor cortex

There is a consensus in the literature that the sheep motor cortex is in the superior frontal gyrus of the frontal lobe and bounded in the rostral-caudal direction by the cruciate sulcus in the frontal lobe and the coronal sulcus in the medial-lateral direction. However, between studies there was large variability in the described functional representation of the motor areas. This can be observed in Fig. 2 and Table 1 where there is great variability between the different studies aiming to generate a functional map of the sheep motor cortex. The most common and consistent responses across studies were those corresponding to the forelimb and in some cases the hind limb. Simpson and King (1911) noted that limb movement could not be generated in all of their 19 animals. Bagley (1922) found that the posterior extremity, to 8 mm anterior to the splenial sulcus, gave rise predominantly to limb movement, with occasional movement in the trunk. Face and head movements varied across studies and between animals within the same study, and these responses were the least common.

Laterality of stimulation responses (ipsilateral or contralateral) were not mentioned in all studies. However, where the laterality was mentioned, contralateral, ipsilateral, or bilateral responses were seen without clearly predictable boundaries. Almost all studies showed variable responses both within repetitions of the experiments in the same animal and between animals in the same studies, and some animals did not show any response to electrical stimulation in the superior frontal gyrus and middle frontal gyrus.

#### 2.2.2. Overt movement responses seen when stimulating outside the motor cortex

Some studies suggested electrical stimulation outside the motor and somatosensory areas generated cortically mediated visible movement responses (Bagley, 1922; Bianchi, 1920; Ziehen, 1899). Simpson and King (1911) suggested that the stimulation seen outside this area was likely due to the spread of current to other areas and not due to focal stimulation of the brain. The suggestion by Simpson and King (1911) that stimulation responses may be caused by the spread of current is plausible. It was also noted that stimulation of many sites of the brain caused movements in all four extremities unless the current was kept at its “lowest”, further adding weight to the theory of current spread (Bagley, 1922). Stimulation parameters such as the polarity of stimulation, location of the return electrode, distance from the target tissue, and the stimulus amplitude all play a vital role in the generation of a response (Ranck, 1975; Sawai et al., 2007; Shivdasani et al., 2010). However, due to a lack of detailed information regarding the electrical stimulation parameters in these papers, it is hard to be certain that responses outside the superior frontal gyrus and middle frontal gyrus were solely due to current spread, but this is possible. Furthermore, connections of the stimulated areas to the motor cortex or subcortical structures are also not known and further confound analysis.

### 2.3. Cytoarchitecture of the sheep motor cortex

The variability in the functional stimulation maps (Section 2.1) can in part be explained by the cytoarchitecture of the motor units in sheep. Of interest are the location and distribution of the pyramidal cells, which are the principal excitable units of the motor cortex and form the corticospinal tract. In this section, we review the studies detailing the histological analysis of the sheep brain with a focus on the motor units and the corticospinal tract.

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