

Long term Vascular Access Ports as a Means of Sedative Administration in a Rodent fMRI Survival Model

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Introduction

The purpose of this study is to develop a rodent survival model that enables fMRI at multiple time-points under sedation. Such a model allows the study of brain plasticity in a single animal over time and reduces the overall number of animals required for longitudinal studies. To date, models within the fMRI literature have required sacrifice of animals immediately following fMRI image acquisition due to the use of paralytic agents and mechanical ventilation (1, 2). Furthermore, in our experience, models using subcutaneous infusion of sedative agents (3) have produced inadequate depth of anesthesia, while the use of repeated tail vein puncture is technically unreliable. Recently, dexmedetomidine (Orion Corp., Espoo, Finland), an alpha-2-adrenergic receptor agonist, has gained acceptance in small animal fMRI literature. Multiple studies have shown delivery of this drug is capable of producing dose-dependent sedation without inhibiting BOLD fMRI signal (3, 4).

Methods

Following an acclimation period of 1 week, 9 Sprague-Dawley rats weighing 150-200g underwent surgical placement of an MRI compatible vascular access port with heparin coating (Harvard Apparatus, Holliston MA). The port itself measures 1cm³ and is composed of a plastic chamber with an overlying silicone diaphragm (Figure 1A). The silicone diaphragm is designed to withstand up to 1000 needle punctures. In each rodent, venous access was obtained through the right femoral vein, where the proximal end of a 3Fr venous catheter was secured in place with two 5-0 silk ties. The distal portion of the venous catheter was then tunneled to the back where it was secured to the vascular access port in a subcutaneous pocket. Slack was maintained in the tunneled line to allow for growth of the animal and to minimize the risk of a potential tethering effect which could dislodge the proximal end of the catheter. Each surgery was performed with the use of Isoflurane 1.4% (Halocarbon Laboratories, River Edge, NJ). Date of port placement was considered week 0.

Animals were then imaged using a Bruker AVANCE 9.4T MRI scanner. The BOLD response to task in the primary sensory and motor regions was studied during median nerve electrical stimulation. To maintain anesthesia during scanning, the vascular port was accessed and a continuous infusion of dexmedetomidine (Orion Corp., Espoo, Finland) was run at a rate of 200mcg/kg/hr (4). During scanning, all animals were allowed to breathe spontaneously through a nose cone with 30%FiO₂. There was no use of mechanical ventilation or paralytic agent. Animal physiology was monitored using continuous pulse oximetry, SAI (Small Animal Instruments) respiratory monitor, and a rectal temperature probe. Each animal underwent imaging at 1 week, 3 weeks, and 5 weeks. Following fMRI, anesthesia was reversed using atipamezole (Orion Corp., Espoo, Finland), given at a dose of 0.1mg/kg IP. The study will be continued to 20 weeks, with imaging at 8 weeks, 12 weeks, 16 weeks, and 20 weeks.

Results

To date, all animals have undergone imaging at 1 week, 3 weeks, and 5 weeks. Image acquisition time is 45 minutes at each time-point. Total time of sedation exceeds 1 hour. While sedated, heart rate ranges from 269-320bpm, with a mean heart rate of 295bpm. Respiratory rate ranges from 43-80 breaths/min, with a mean respiratory rate of 62 breaths/min. Pulse oximetry has ranged from 98-99%. There have been no episodes of hypoxemia or apnea. All vascular access ports have remained patent. Patency is determined by ease of injection, adequacy of and ability to obtain general anesthesia, and physical exam of the port site. BOLD response to median nerve stimulation was identified within the contralateral S1FL region at each time-point.

Discussion

What is lacking in fMRI literature is a robust, reproducible model by which an animal can be safely sedated and recovered to allow for fMRI image acquisition at multiple time-points. It is promising that all vascular access ports have remained patent 5 weeks after surgical placement, and all animals have been safely sedated using continuous infusion of dexmedetomidine without the requirement of mechanical ventilation or a paralytic agent. Furthermore, the use of MRI compatible vascular ports provides a means access which can be applied to fMRI survival models requiring contrast administration, repeated blood sampling, or the use of multiple intravenous medications.

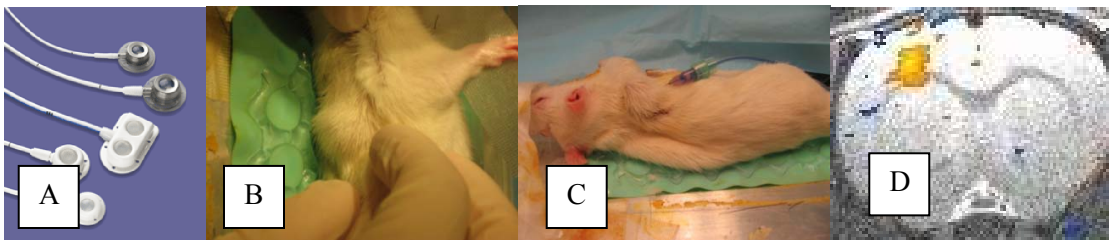


Figure 1 A. Vascular access ports. B. Port placed in subcutaneous pocket within the back, 1 week post-operatively. C. Port accessed with MRI compatible Huber needle. D. Contralateral activation in S1FL region with median nerve stimulation.

References

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