Cerebral Activation During the Test of Spinal Cord Injury Severity in Children: an fMRI Methodological Study

Laura Krisa, PhD,¹ Devon Middleton, MS,² Scott Faro, MD,² Christina L. Calhoun, MSPT,¹
Feroze B. Mohamed, PhD,² and M.J. Mulcahey, PhD, OTR/L^{1,3}

¹Shriners Hospitals for Children, Philadelphia, Pennsylvania; ²Temple University School of Medicine, Philadelphia, Pennsylvania;

³Jefferson School of Health Professions, Thomas Jefferson University, Philadelphia, Pennsylvania

Background: The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) are internationally accepted to determine and classify the extent of motor and sensory impairment along with severity (ASIA Impairment Scale [AIS]) following spinal cord injury (SCI). The anorectal examination is a component of the ISNCSCI that determines injury severity. There is a void in the health care literature on the validity of the anorectal examination as an indication of SCI severity. **Objective:** To validate the use of functional magnetic resonance imaging (fMRI) for the purpose of classifying the severity of SCI in children. **Methods:** Seventeen patients, with the average age of 14.3 years, underwent 1 complete ISNCSCI examination. Subjects also underwent the anorectal portion of this exam while fMRI data were collected using a 3.0 Tesla Siemens Verio Scanner. Cortical areas of activation were analyzed for possible differences of cortical involvement between complete (AIS A) and incomplete (AIS B, C, and D) SCI subjects. Anxiety/anticipation of the test was also assessed. **Results:** This study established an fMRI imaging protocol that captures the cortical locations and intensity of activation during the test of sacral sparing. In addition to developing the data acquisition protocol, we also established the postacquisition preprocessing and statistical analysis parameters using SPM8. **Conclusion:** Preliminary findings indicate that fMRI is a useful tool in evaluating the validity of the anorectal examination in determining SCI severity. Assessment of which cortical regions are activated during the testing procedure provides an indication of which pathways are transmitting information to the brain. **Key words:** functional magnetic resonance imaging, International Standards for Neurological Classification of Spinal Cord Injury, pediatric, spinal cord injury

There are approximately 12,000 new cases of spinal cord injury (SCI) each year in the United States, with a current estimate of 270,000 people living with SCI in the United States alone.¹ Roughly 20% of reported SCIs are in people between the ages of 0 and 20 years old.² SCI can have important developmental, psychological, and physiological consequences on the pediatric population,³ therefore it is particularly important to accurately classify the injury severity of SCI in children and youth so that an accurate prognosis can be made and proper treatment and therapy can be defined.

The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) are internationally accepted to determine and classify the neurological consequence of SCI.⁴ The neurological assessments, which include motor, sensory, and anorectal examinations, provide the basis for classifying the neurological level, motor scores and motor level, sensory scores and sensory level, zone of partial preservation, and degree of

impairment or severity of the SCI.⁴ The anorectal examination, which includes appreciation for deep anal pressure (DAP) and voluntary anal contraction (VAC), is a component of the ISNCSCI that contributes to the determination of injury severity (complete/incomplete). Despite the widespread use of the anorectal examination, there is a void in the health care literature on the validity of the anorectal examination as an indicator of SCI severity.

Until the seminal work by researchers at the Shriners Hospitals for Children,^{5,6} the reliability and utility of the ISNCSCI when applied to children was unknown. Mulcahey et al⁷ were the first to report on the ISNCSCI in children and found strong agreement on repeated motor and sensory scores for children older than 4 years of

age; further research with a larger sample and additional raters was suggested. More recent work^{5,6,8,9} had similar findings with respect to the reliability of the motor and sensory examinations but with an unacceptably low agreement for results of the anorectal examination. A closer comparison of the anorectal examination with MRI findings resulted in even more concern in regard to the validity of the anorectal examination, as one case illustrated complete transection of the cord by MRI but was classified as an incomplete SCI by the ISNCSCI.¹⁰

In the absence of S4/5 pin prick (PP; discrimination between the sharp and dull side of a safety pin) and light touch (LT) sensation in the S4-S5 dermatome, the test of DAP is necessary to determine whether the subject is sensory incomplete. However, there are a number of studies that indicate the presence of an alternative pathway that is responsible for the perception of sensation below the level of the lesion in subjects with a complete transection of their spinal cord and clinically labeled as a complete SCI.^{6,11-14} In addition, earlier work conducted in the pediatric SCI population^{6,15} reported participants describing a variety of sensations during the test of DAP including general warmth throughout their body, headaches, tingling throughout the body, and goose bumps.

The primary objective of this study was to develop, solidify, and test a functional magnetic resonance imaging (fMRI) protocol, based on blood oxygenation level dependent imaging (BOLD), that captures the cortical locations and intensity of activation during the test of DAP, VAC, and S4/5 sensations in children and adolescents with SCI. Within this objective, we did not focus on obtaining data for statistical analysis and comparisons among groups but rather on developing the best imaging protocol that can be used in future studies to assess the validity of the anorectal examination in the pediatric SCI population and the challenges of imaging this population. This study is a necessary step for establishing an imaging protocol that can be used as a neurodiagnostic tool to determine whether the anorectal examination is a valid indicator of injury severity in youth and adolescents with SCI.

Methods

Research design

This was a cross-sectional fMRI study conducted at Shriners Hospitals for Children, Philadelphia. The study was reviewed and approved by the institutional review board. Written informed consent was obtained from parents or legal guardians of all participants who were under 18 years of age. Participants who were between 7 and 17 years of age also provided written informed assents.

Sample

A sample of 17 participants who were between 7 and 21 years of age with chronic SCI (>3 months post injury) were included in this study. At the time of the study, all were receiving routine orthopedic and rehabilitation treatment for chronic SCI. Children were not invited to participate if they had concomitant brain injuries resulting in the cognitive inability to participate in the ISNCSCI, were sustained by mechanical ventilation, experienced dysreflexia during the anorectal examination, contained magnetic medical implants or metal fragments or had medical problems that would inhibit placement in the scanner, could not click a computer mouse, or refused to sign written informed consent and assent.

Data collection

ISNCSCI examination

Subjects underwent 1 complete ISNCSCI examination (motor, sensory, and anorectal exam) and were scored according to the 2003 ISNCSCI standards.⁴ The anorectal examination was performed according to the standards of the ISNCSCI and according to a previous publication.⁶ DAP was determined by applying pressure to the rectal wall with the index finger (for a minimum of 3 times) and was scored as intact sensation if the subject responded “yes” each of the 3 times. VAC was evaluated by asking the subject to squeeze the examiner’s finger while it was inserted in the anus “as if to hold in a bowel movement.” During the test for VAC, subjects were instructed not to

increase intra-abdominal pressure by holding their breath or tightening their abdominal muscles.

fMRI data collection

Each subject was positioned in a partial side-lying position on the scanner table. Special care was taken to ensure the subject's head was flat and able to fit comfortably in the head coil with minimal movement. Extra table padding and pillows were used to ensure the subject was comfortable and to prevent skin breakdown. Ear plugs were placed in the subject's ears for protection, eye goggles were placed over the eyes for visualization cues, and the head coil was then put in place. In addition, the subject's blood pressure was monitored throughout the study.

Subjects completed 2 fMRI scans 2 to 48 hours apart while undergoing the sacral sparing component of the ISNCSCI. This included DAP, VAC, and PP and LT appreciation at the S4/5 dermatome. A sterile plastic toothpick replaced the metal pin that is typically used for this exam because it is not magnetic resonance compatible. Due to the inability of the subjects being able to speak while in the MRI scanner, they were not tested for sharp/dull discrimination as is done during the standard ISNCSCI exam; they were only tested for their ability to perceive sharp sensation. During the test of DAP and VAC, subjects were also tested for their anticipation of the stimulus. A green square seen in the goggles indicated no pressure against the rectal wall or contraction of their rectal muscle. A red square indicated that the rectal wall would be stimulated (they were not told when) or that they would be asked to contract their rectal muscle. Each colored square was presented for 40 seconds; the first 20 seconds of each colored square presentation was used for anticipation data analyses, which also represented the rest condition, and the second 20 seconds was used to assess cortical areas of activation due to either DAP or VAC.

Experimental design

Anorectal component

The subjects underwent 2 blocks assessing anorectal function (**Figure 1A**) – one assessed

cortical activation during rectal wall stimulation while the other examined cortical activation during anal contraction. The index finger was inserted in the rectum prior to any fMRI recordings. Every 80 seconds, pressure was applied to the rectal wall or the subjects contracted their rectal muscle. The pressure application or contraction lasted 3 seconds, but data collection continued for the next 17 seconds. This was done consecutively 3 times; each data collection block lasted 4 minutes.

S4/5 dermatome testing

The left and right S4/5 dermatome was tested for LT and PP responses (**Figure 1B**). For LT, a 100-second baseline measure was collected prior to swiping a cotton swab 10 times (10 seconds apart) on the right and left side of the buttocks. The same experimental design occurred for the collection of PP data, except a plastic toothpick replaced the cotton-tipped applicator. For all components of the stimulation paradigm (excluding anorectal contraction), subjects clicked a mouse connected to the imaging software if they felt stimulated. For anorectal contraction, the therapist performing the rectal examination noted whether contraction around their finger occurred.

Data acquisition

The BOLD-fMRI of the whole brain was acquired with a commercial 3.0 Tesla Siemens Verio Scanner (Siemens Vision, Erlangen, Germany) using echo planar imaging capability (EPI: 30 axial slice of 5 mm slice thickness; field of view [FOV] = 220 mm; repetition time [TR] = 3 seconds; echo time [TE] = 54 ms) and a 12-channel phased array brain coil. High resolution T1-weighted structural images were also acquired following the same slice prescriptions as the functional images for accurate anatomical co-registration and segmentation. The stimulus was presented using a high resolution goggle/projector system that was controlled through a laptop from outside the scanner using Presentation software (Neurobehavioral Systems, Albany, CA). The stimulus timing was synchronized with the scanner acquisition timings.

Figure 1. Experimental design. (A) Protocol used during the anorectal examination during fMRI imaging. This design was used for both deep anal pressure and voluntary anal contraction. (B) Protocol used for S4/5 dermatome testing.

Results

Over the past 2 years, we pilot tested several variations of this imaging protocol (**Figure 1**) in 17 children and adolescents with SCI (American Spinal Injury Association Impairment Scale [AIS] A=4, B=9, C/D=4). This study resulted in an established fMRI imaging protocol that captures the cortical locations and intensity of activation during the test for sacral sparing including DAP and S4/5 PP and LT sensory appreciation. In addition to developing the data acquisition protocol, we established the postacquisition preprocessing and statistical analysis parameters using SPM8 (Wellcome Department of Cognitive Neurology, University College of London, UK) run under the Matlab (The Mathworks, Inc., Natick, MA) environment. **Figure 2** illustrates fMRI pilot data obtained from 3 subjects with different AIS classifications. These data show differences in the cortical areas activated during DAP, LT, and PP. During this feasibility study, we did not aim to obtain an equal number of subjects with complete, motor incomplete, and sensory incomplete SCI, therefore we do not have statistics calculated for this study yet.

We also collected imaging data during the test of VAC. However, due to difficulties in timing data collection accurately during anal contraction, we were unable to obtain usable imaging data for analysis. We found, on a first-level analysis, that a greater number of subjects showed activation in the frontal cortex during the anticipation of DAP ($n = 12$) when compared to DAP stimulation ($n = 6$) (data not shown).

Discussion

This is the first study to develop and test an fMRI imaging protocol that can be used to examine the test of sacral sparing in children and adolescents with SCI. The ISNCSCI manual suggests that the presence of DAP is the only way to determine a sensory incomplete SCI in the absence S4/5 sensation. However, there is a void in research evidence on the validity of the anorectal examination. The lack of validity studies on the anorectal examination may be due to the invasive nature of this exam or a lack of an alternative method to evaluate the severity of an SCI or a combination of both.⁶

Figure 2. Primary areas of activation during components of the test of SCI severity among individual subjects categorized as AIS A, B, and D according to the ISNCSCI criteria. Examples are based on single subject results. AIS A = complete; AIS B = sensory incomplete; AIS D = motor incomplete; DAP = deep anal pressure, LT-R = light touch (cotton swab) right side; PP-R = pin prick (plastic toothpick) right side. $P = .05$.

Although it is important to develop the proper method to accurately determine injury severity among all ages, the use of neurodiagnostic adjuncts to the clinical assessment is extremely important within the pediatric population due to the cognitive requirements of the testing procedure. For example, regardless of their age at the time of the anorectal examination, children who are injured

prior to achieving bowel continence may lack the essential experiences or mental representations to respond to the test instructions “squeeze as if to hold in a bowel movement” or “tell me when you feel pressure.”⁶ Moreover, 6 years of age was found to be the youngest age at which children were able to follow test instructions when sharp/dull discrimination and light touch were applied to

their cheek to demonstrate what “normal” should feel like.⁸ Mulcahey et al.¹⁶ reported that children as young as 6 years should be evaluated based on the ISNCSCI standards but also cautioned that children as old as 10 years may have difficulty with the testing procedures. Although children and youth represent a relatively small segment of the population with SCI, their neurologic evaluation should be undertaken with instruments and methods that are valid and produce reliable data. Without such instruments and methods, little credence can be placed on studies that report that children have more neurologic recovery than adults and studies that report on treatment effectiveness of therapies that claim to aid in motor and sensory functions.

This study established an imaging protocol that will be used in future studies to compare the differences in cortical areas of activation in subjects with different AIS classifications (complete, motor incomplete, sensory incomplete) in the pediatric SCI population. This study also revealed the challenges that occur during imaging data collection within this unique population.

First, we found that children under 10 years of age have a difficult time remaining still for an extended period of time in the scanner. Total time for data collection for this study was 40 minutes. However, to ensure the safety of the subject, we spent an additional 10 to 15 minutes making sure the subject was comfortable and extra padding and pillows were in place to prevent skin breakdown and establishing a baseline blood pressure prior to the start of data collection. Additionally, these young children often requested that their parent/caregiver remain in the scanner room during testing, which often resulted in the children becoming distracted and/or over-clicking the mouse during sensory testing even when the stimulus was not being presented. The latter is thought to be due to the children's desire not to disappoint their parent/caregiver if they were not able to feel the stimulation. The study's instructions and procedure were reviewed prior to the participants entering the scanner and also during the study, but some participants had trouble understanding the instructions.

Second, to gain access to the anorectal region, subjects were placed in a partial sidelying position. Although this position works well for some subjects, other subjects are unable to keep this position due to hip contractures, spinal fusions, or leg spasms. In addition to leg spasms, some subjects had spasms during the anorectal examination due to stimulation. Depending on the flexibility of the subject's hips and spine, the head is often turned to the side to off-set the lack of flexibility, which leads to a challenge when processing the data.

Last and most important, subjects of this age range have a difficult time remaining still during the data collection procedure, resulting in a large degree of head motion in roughly 50% of the population scanned. Due to the small sample size of this population, it is important to ensure the subjects remain as still as possible so that data do not need to be discarded due to excessive movement.

In most cases, subjects who were injured prior to or during their adolescent years have spinal instrumentation to correct for scoliosis. In the majority of patients with spine fusions, the metal used is MRI compatible. However, subjects who had 2 or more cross-links or wires attached to the fusion rods that complete a circuit are not able to participate in the study due to the possibility of internal heating.

As previously mentioned, we collected fMRI data during the test of VAC and prior to the stimulus being delivered during DAP and before VAC to assess the anticipation of the stimulus. To achieve accurate imaging data during the test of DAP, the use of anorectal manometry is required to accurately time the motor contraction with the cortical activation. Although the use of anorectal manometry is feasible, it will add additional time to the length of the scan. First-level analysis results showed a number of cortical areas of activation that varied among subjects during the anticipation of either DAP or VAC. However, there was a large amount of activation in the prefrontal cortex during DAP anticipation. Similar results were found by Wietek et al.¹⁴ during rectal stimulation in subjects with AIS A SCI. The prefrontal cortex was the only region that

showed significantly higher activation compared to the healthy group. This is attributed to the possibility that mental imagery occurred with the anticipation of the stimulus.

To address these challenges, we designed a new imaging protocol that is shorter in duration and focuses data collection on DAP and S4/5 dermatome sensory testing. Initially, we will only include subjects between the ages of 10 and 21. However, once we optimize the data collection procedure and simplify the testing directions, we will include subjects as young as 6 years old. If a subject is unable to keep a partial side-lying position, we will collect the data in supine with both legs elevated and supported with additional padding. To aid in preventing head movements, a Vacuform hood (Cambridge Research Systems, England) will be placed around the subject's head. In addition, we have established the postacquisition preprocessing and statistical analysis parameters using SPM8 (run under the Matlab environment). Using this software, we will rigorously evaluate motion in these subjects prior to applying head motion correction algorithms.

Conclusion

We established, validated, and tested a BOLD-fMRI imaging protocol that can be used to capture the cortical locations and intensity of activation during the test of DAP and S4/5 sensations in children and adolescents with SCI. We have demonstrated the feasibility of obtaining fMRI data in subjects with different AIS classifications. In addition, we summarized the challenges that occur when conducting a study of this nature within the pediatric SCI population. This protocol needs to be applied to subjects with different AIS classifications, and data need to be statistically analyzed and compared among groups to aid in validating the anorectal examination as an indicator of SCI severity.

Acknowledgments

This study was funded by the Shriners Hospitals for Children Research grant 8509 (L. Krisa, PI).

REFERENCES

1. The National SCI Statistical Center. Spinal Cord Injury Facts and Figures at a Glance. February 2012. https://www.nscisc.uab.edu/PublicDocuments/fact_figures_docs/Facts%202012%20Feb%20Final.pdf.
2. Mad Spaze Club Pediatric Spinal Cord Injury MSC Web Designs. <http://www.streetsie.com/pediatric-spinal-cord-injury/>.
3. Parent S, Mac-Thiong JM, Roy-Beaudry M, Sosa JF, Labelle H. Spinal cord injury in the pediatric population: a systematic review of the literature. *J Neurotrauma*. 2011;28(8):1515-1524.
4. American Spinal Injury Association. *Reference Manual for International Standards for Neurological Classification of Spinal Cord Injury*. Chicago: Author; 2003.
5. Mulcahey MJ, Gaughan J, Betz RR. Agreement of repeated motor and sensory scores at individual myotomes and dermatomes in young persons with complete spinal cord injury. *Spinal Cord*. 2009;47(1):56-61.
6. Vogel L, Samdani A, Chafetz R, Gaughan J, Betz R, Mulcahey MJ. Intra-rater agreement of the anorectal exam and classification of injury severity in children with spinal cord injury. *Spinal Cord*. 2009;47(9):687-691.
7. Mulcahey MJ, Gaughan J, Betz RR, Vogel LC. Rater agreement on the ISCSCI motor and sensory scores obtained before and after formal training in testing technique. *J Spinal Cord Med*. 2007;30(suppl 1):S146-149.
8. Chafetz RS, Gaughan JP, Vogel LC, Betz R, Mulcahey MJ. The International Standards for Neurological Classification of Spinal Cord Injury: intra-rater agreement of total motor and sensory scores in the pediatric population. *J Spinal Cord Med*. 2009;32(2):157-161.
9. Mulcahey MJ, Gaughan JP, Chafetz RS, Vogel LC, Samdani AF, Betz RR. Interrater reliability of the International Standards for Neurological Classification of Spinal Cord Injury in youths with chronic spinal cord injury. *Arch Phys Med Rehabil*. 2011;92(8):1264-1269.
10. Samdani AF, Fayssoux RS, Asghar J, et al. Chronic spinal cord injury in the pediatric population: Does magnetic resonance imaging correlate with the International Standards for Neurological Classification of Spinal Cord Injury examination? *Spine (Phila Pa 1976)*. 2009;34(1):74-81.
11. Finnerup NB, Gyldensted C, Fuglsang-Frederiksen A, Bach FW, Jensen TS. Sensory perception in complete spinal cord injury. *Acta Neurol Scand*. 2004;109(3):194-199.
12. Sherwood AM, Dimitrijevic MR, McKay WB. Evidence of subclinical brain influence in clinically

- complete spinal cord injury: discomplete SCI. *J Neurol Sci.* 1992;110(1-2):90-98.
13. Dimitrijevic MR. Neurophysiology in spinal cord injury. *Paraplegia.* 1987;25(3):205-208.
14. Wietek BM, Baron CH, Erb M, et al. Cortical processing of residual ano-rectal sensation in patients with spinal cord injury: an fMRI study. *Neurogastroenterol Motil.* 2008;20(5):488-497.
15. Mulcahey MJ, Gaughan J, Betz RR, Johansen KJ. The International Standards for Neurological Classification of Spinal Cord Injury: reliability of data when applied to children and youths. *Spinal Cord.* 2007;45(6):452-459.
16. Mulcahey M, Vogel L, Betz R, Samdani A, Chafetz R, Gaughan J. The International Standards for Neurological Classification of Spinal Cord Injury: psychometric evaluation and guidelines for use with children and youth. *Phys Med Rehabil.* 2011;92:1264-1269.