A New Measure of Hand and Forelimb Function after Cervical Spinal Cord Injury in Rats

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by

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Abstract

Approximately 12,000 new traumatic spinal cord injuries (SCI) occur per year in the US. Half of these injuries occur in the neck or cervical region, which impairs hand function. In animals with SCI, few reaching and grasping tests exist for bimanual manipulation or complex coordinated digit, forearm, and wrist movement. The objective of this experiment was to identify differences in movement, manipulation, and coordination of forelimb function after cervical SCI using elbow pasta. Adult Sprague-Dawley rats were randomly assigned into naive (n=3), mild (n=6), and severe (n=5) groups with a spinal contusion centered at C5. Injury severity was controlled using the Infinite Horizon (IH) impact device. The device is capable of producing graded magnitudes of injury (125 IH for mild, 175 IH for severe) by changing the force applied to the stabilized spinal column and exposed spinal cord. The experiment was set up to produce outcomes that are both sensitive to injury severity and recovery time tested at 7-70 d post SCI, 1 day/wk. In one session, rats were videotaped eating pasta in an enclosed area and paw and forelimb function was evaluated. Normal movements (digit and forelimb release and regrasp of the pasta) declined after mild SCI and severe SCI. Abnormal movements (fail to release or regrasp pasta and little digit movement) increased after mild SCI and severe SCI. This study provides evidence that using elbow pasta is a valid test to measure hand and forelimb function and can be used as a tool to evaluate SCI in rats. Thus, the elbow pasta test is a valid, sensitive tool which detects normal and abnormal bimanual function after SCI. It may offer better discrimination of efficacy for preclinical agents given its ability to measure both function and deficits.
Introduction

The spinal cord can be divided into four parts: cervical (8 vertebra), thoracic (12), lumbar (5), and sacrococcygeal (6). The spinal cord (which is comprised of nerves which act as the communication system for the body) relays information from the body to the brain and receives efferent commands from varied portions of the brain. This study focuses on the cervical spinal cord region, primarily C5 (where the contusion was centered). The eight cervical spinal cord nerves innervate the muscles of the head, neck, upper body, arms, and hands. C1 and C2 control the head and neck, C3 controls the diaphragm, C4 controls the upper body muscles, C5 and C6 control the wrist, and C7 and C8 control the hands (McKinley, 2002).

In the spinal cord, gray matter is surrounded by white matter at its circumference which is made up of myelinated axons, while the gray matter contains neuronal cell bodies and can be divided into the dorsal horn, intermediate gray, ventral horn, and centromedial region surrounding the central canal (McKinley, 2002). The ventral horn and roots contain the motor neurons and axons respectively which control the muscles of the arm and hand. Nerve impulses are transmitted from the spinal cord to the skeletal muscles. There is an integration of descending commands from the brain for movement, transmitted through synapses to interneurons and to motor neurons. The motor neurons fire and cause muscle contraction. Dorsal roots contain sensory nerve fibers, transmitting nerve impulses from peripheral regions to the spinal cord through an integration of ascending commands.
Spinal cord injury (SCI) refers to any injury of the neural elements within the spinal cord (Overview: SCI Anatomy and Physiology). Injuries to the cervical spinal cord occur 51.7% of the time with the most common injury at the lower part of the neck: C4, C5, and C6 levels (Overview: SCI Anatomy and Physiology). After SCI, both sensory and motor functions are affected. At the time of injury, neurons, glia, and blood vessels experience immediate damage. Following this primary injury, secondary injury takes place and is often responsible for most of the function deficits in people with SCI (Overview: SCI Anatomy and Physiology). The progression of secondary injury can vary greatly depending on the severity of injury. In a mild injury, in this case at C5, secondary injury begins with bleeding in the central gray matter (in a mild injury, SCI effects are isolated to the gray matter but bleeding can extend slightly into the white matter). Ischemia, reduction of blood flow, and edema occur as well. (Overview: SCI Anatomy and Physiology). The combination of these three events leads to tissue death which can extend one segment above and below the site in a mild injury. In a severe injury, the same primary and secondary injuries take place at a faster rate, and tissue death can encompass the entire gray matter, a large portion of the white matter, and one to three segments above and below the injury site (Overview: SCI Anatomy and Physiology).

After a C5 spinal cord injury, there are functional deficits and/or a complete loss of function below the level of injury depending on the severity of injury. Complete personal assistance may be required when arm function is lost as occurs with a C5 injury. The person will need assistance with washing, dressing, and assistance with bowel and bladder management. Complete domestic care is required, such as household cleaning, washing
of clothes, kitchen duties, and preparation of meals (National Institute of Neurological Disorders and Stroke, 2010). In contrast, a C7 or C8 injury results in partial finger movement and full wrist extension and flexion. A person with preservation of C7/8 function would be able to feed themselves and perform in bowel and bladder management independently. Upper body showering and dressing as well as the ability to prepare simple meals and perform simple household duties could be done independently as well (National Institute of Neurological Disorders and Stroke, 2010). Thus, research that could restore the function of the spinal cord a couple of segments below the site of injury would greatly improve a person’s quality of life. According to a survey done by Anderson (2004) in which subjects were asked to rank seven functions in order of importance to their quality of life, 48.7% of tetraplegics indicated that regaining arm and hand function would improve their quality of life. This need stresses the importance to use cervical SCI models that implement behavioral tests that are sensitive to bimanual forearm and forepaw manipulation. Assessing this key feature of manipulation is important because it is seen in everyday human tasks such as folding laundry, using a can opener, or tying shoelaces. These tests can be used as a tool to validate the efficacy of future treatments and therapies directed toward improving the quality of life for the more than 200,000 people living with SCI.

The experimental contusion model for SCI used in rodents closely replicates the mechanism of injury in humans (Bunge, 2005). Rats are particularly useful as a neurological model because rodents use their forelimbs in some ways that are homologous to humans such as lifting the limb and advancing it toward the food source,
pronating the paw/hand over the food source, and withdrawing the limb. (Whishaw, 1992; Cenci 2002). There are also similarities in the adjustments made by the limb to manipulate the target object (Whishaw, 1992).

To date, a variety of tests have been developed to assess forelimb function in rats after cervical SCI. These tests include food pellet reaching and retrieval tasks (Castro, 1972; Whishaw et al., 1990) in which the test evaluates grasp execution and retrieval performance of a single limb. The matrix reaching test (Ballermann et al., 2001) quantifies the reaching path a single limb executes as it breaks individual pasta pieces out of a matrix and the staircase test (Montoya et al., 1991) focuses on pellet retrieval from different stairs with the forelimb in a pendant position. The angel hair pasta test (Whishaw, 1996) and the Vermicelli Handling Test (Allred, 2008) measures the number but not the type of forelimb adjustments as the pasta is eaten. The grip strength test (Dunnett, 1988) measures digit strength. While current tests provide measurements of forelimb function, they fail to assess bimanual manipulation. Also many available tasks focus mainly on the reaching aspect of forelimb function. There is a lack of tests that measure manipulation independently from reaching movements.

Paw use and manipulation significantly correlate with the shape of food (Whishaw et al., 1996). Uninjured rats display complex coordinated movements while using their paws and digits to manipulate the food. SCI can have a strong influence in the way rodents use their digits. Therefore, the purpose of this experiment was to use elbow pasta as a tool to identify and define patterns of normal versus abnormal bimanual digit, forelimb, and wrist
movement and was set up to see if elbow pasta is a viable tool to measure both function and deficits after cervical SCI which could be used as a tool to evaluate the efficacy of preclinical agents or therapies.

**Materials and Methods**

**Subjects**

Fourteen adult female Sprague-Dawley rats (220-244 g) were used in this study. The rats were randomly assigned to one of three groups: naive (n=3), mild (n=6), and severe (n=5). The rats were housed two to three per cage, exposed to a 12 hour light/dark cycle, and had food and water ad libitum. The Ohio State University Laboratory Animal Care and Use Committee approved all procedures for these experiments.

**Stimuli**

Rats were given uncooked elbow macaroni (Barilla elbows, ridges with a 90° twist, which gives the pasta a more complex shape) with a weight of 0.3g (Figure 1). Ingredients (provided by the manufacturer) were: semolina, niacin, ferrous sulfate, thiamine mononitrate, riboflavin, folic acid (calories per gram: 3.6, total fat/gram: 0.018, total carbohydrate/gram: 0.75, total protein/gram: 0.125). Prior to the onset of testing, rat chow was removed for a few hours to motivate spontaneous eating. The shape of the pasta allows for the evaluation of the rats’ ability to use both gross and fine motor control as well as their ability to coordinate bimanual manipulation.
Figure 1. Uncooked Barilla elbow macaroni.  **A.** Whole pasta defined as Large for this study.  This type of elbow pasta has an extra twist added to the typical elbow macaroni shape.  **B.** The pasta is half its size and is defined as Small in this study.  Scale is shown in inches.

**Surgical procedures**

Spinal cord contusion surgeries were performed on the mild and severe groups.  Anesthesia was given by an intra-peritoneal injection of ketamine (80 mg/kg) and xylazine (10 mg/kg) and given prophylactic antibiotics (gentomycin sulfate, 1 mg/kg) subcutaneously.  An incision was made along the dorsal part of the neck and the spinous process of C5 was removed to expose the cord.  Contusion injuries were produced using the Infinite Horizon controlled impact device (Precison Systems and Instrumentation, LLC, Lexington, KY, USA) which produces a graded magnitude of injury as a result of defined changes in the amount of force applied to the rigidly stabilized spinal column and exposed spinal cord.  Animals were secured in place with spinous process clamps at C4 and C6.  A rapid 125 kDyne (mild injury) or 175 kDyne (severe injury) displacement of the cord was performed.  Once the surgical procedure was complete, the muscle tissue was sutured and the skin closed with wound clips.  Normal saline (5 cc.) was given subcutaneously to prevent dehydration.  The rats were placed in an incubation chamber maintained at 37°C for recovery.  Over a ten week period, the rats were weighed at least weekly and were
provided food supplements as necessary to maintain weight and were later perfused with 4% Para formaldehyde. The spinal cord tissue was stored for future lesion verification.

**Behavioral Testing**

*Elbow pasta test.* Video recording was done with a Sony HDR-SR11 video camera. The tapes were replayed for analysis of each forelimb in slow motion (0.33x) using Video LAN VLC Media Player. Individual rats were placed in a clear Plexiglas box (10 cm wide, 17 cm deep, and 13.5 cm tall) mounted on a glass floor under which was an inclined mirror to facilitate filming from a ventral view. The pasta was placed on the floor of the box. The rats were videotaped during spontaneous eating at 1, 2 and 10 weeks post operatively.

**Adjustment episodes**

One episode consisted of a rat eating an entire, or close to entire, piece of elbow pasta in view of the camera. The movement patterns and wrist movement were tallied while watching the video playback in slow motion (0.33x). The left and right paw movement patterns and wrist movement were kept separate. Some of these patterns were influenced by the size of the pasta: large, whole pasta versus less than half the size of the elbow pasta. Therefore, an episode was divided into 2 phases: the first was when the pasta was large (bigger than ½ the size), the second phase started when the pasta was clearly less than ½ the size. Episodes were ignored if the rat did not finish eating the pasta or if the digits and/or forelimb could not easily be seen. Data was collected without knowledge of experimental condition. The primary quantitative variable recorded for forelimb manipulation was the number of adjustments made with each forelimb per pasta piece. An
adjustment was defined as any visible release-regrasp of the pasta piece or reformation of the paw hold on the pasta piece using extension/flexion and/or abduction/adduction of the digits (Allred et al., 2008). Only adjustments made after eating had started and in the paws’ contact with the pasta piece were counted. The primary quantitative variable recorded for wrist movements was the number of movements made with each wrist per pasta piece. Movement is defined as a visible flexion, extension, rotation inward/outward of the wrist. Passive wrist movement that was caused by the movement of the pasta was ignored. Only movements made after eating started were counted. Eating behavior was also timed for each episode from the point at which the rat took the first bite of the pasta until the pasta was clearly ½ the size. The second phase time started when the pasta piece was ½ its size until consumption of the pasta piece was completed. Time was stopped if the pasta piece was dropped.

**Statistical Analysis**

Behavioral data were analyzed with the nonparametric Mann-Whitney U test because data was missing for some rats on some testing days. The 2-tailed Mann-Whitney U was used to compare group (naive, mild, and severe) and size (large or small pasta) by week. Right and left paw and large and small pasta measures were kept separate unless specified. Statistical analysis could not be performed for week 1 severe group data because the severe group had only 1 rat that performed the task during week 1. All descriptive statistics are reported as percent movement means ± standard error mean unless otherwise noted. Significance was determined *a priori* at p < 0.05.
Results

The number of rats that completed the task at time point varied within each group (Table 1). The rats were not pretrained with elbow pasta and mild or no food deprivation was used. Therefore, it is not known whether the rats (especially the severe group) during week 1 would not eat the pasta or physically could not eat it. Also, throughout the study, some rats within each group chose not to eat the pasta at every time point.

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Table 1. Rat numbers for each week. Numerator = number of rats that completed the task; denominator = number of rats per group.

Normal and Abnormal Bimanual Movement Patterns

The following Normal Movement Patterns were documented:

1. Digit and forelimb release and regrasp (D+F R/R): extension of the digits to release the pasta and simultaneous forelimb movement away from the pasta piece, then flexion of the digits to regrasp the pasta while the forelimb is moving back to the pasta piece (Figure 2 A,B,C).

2. Digit only release and regrasp (D only R/R): extension and flexion of the digits to release and regrasp the pasta while the forelimb is stationary (Figure 2 D,E,F).
Figure 2. Examples of normal movement patterns. Each row is an example of paw position before, during, and after the movement. The adjusting paws are indicated by asterisks. A-C: digit and forelimb release and regrasp. D-E: digit only release and regrasp.

These first two patterns were defined as normal movement patterns because these patterns are primarily or exclusively used by normal rats to manipulate the elbow pasta.

The following Abnormal Movement Patterns were documented:

1. Forelimb only release and regrasp (F only R/R): The digits are fixed in a curved (C-shaped) position, but are able to release from the pasta, while the forelimb simultaneously moves away from the pasta. Regrasp is performed by the forelimb moving back to the pasta piece without digit flexion (Figure 3 A,B,C).

2. Fail to release: The digits are fixed in a flexed position around the pasta and do not release the piece so the forelimb movement (direction indicated by arrow) is stunted (Figure 3 D,E,F).

3. Fail to regrasp: The digits are fixed in a fist position, therefore the digits are unable to extend to regrasp the pasta after the forelimb has simultaneously
moved away from and back to the pasta piece (Figure 3 G,H,I).

Figure 3. Examples of abnormal movement patterns. Each row is an example of the paw position before, during, and after the movement. The adjusting paws are indicated by asterisks. **A-C:** forelimb only release and regrasp. **D-F:** fail to release. **G-I:** fail to regrasp.

These last three patterns were defined as abnormal movements because of the inability to use digit movement to help manipulate the elbow pasta.

Both right and left paws made adjustments while eating. There was no evidence for a dominant “grasp” paw which would help stabilize the pasta piece or a dominant “guide” paw which would make the majority of adjustments as seen in the vermicelli handling tests.
performed by Allred et al., 2008. There was evidence for bimanual manipulation in which there is dual forelimb/digit movement simultaneously exhibited by both paws.

By classifying and measuring each movement pattern, a clear picture of lingering deficits post cervical SCI can be obtained (Figure 4). Because the contusion was centered at C5, the right and left paw percent movement patterns were averaged together. The frequency of both normal and abnormal movement remains fairly stable across all time points. Normal movements (Figure 4A) show a clear and significant decrease ($p<0.05$) as injury severity increases. Abnormal movement increases as injury severity increases (Figure 4B).

Separating measures of the right and left paw (Figure 5) validates the position of the lesion (centered at C5) since there is no significant differences between the left and right paw. The separation also puts the focus on bimanual manipulation. There is an absence of a dominant paw, both the right and left forelimbs are required to manipulate the pasta piece regardless of pasta size. The respective groups (naive, mild, severe) function did not change significantly from week 1 to 10.

The raw data (number of adjustments per pasta piece) can be seen in Table 2. There are significant differences between naive and mild in all three time points. Also there were significant differences between naive and severe during week 2 and 10. Week 1 severe group could not be analyzed because only one rat performed the task.
By separating both the normal and abnormal movement patterns into each individual eating pattern, the trends still hold true. For the two movement patterns characteristic of normal bimanual function (Figure 6), frequency of each movement is inversely proportional to injury severity. The mild, small pasta group had significant differences over time (week 1 vs. 2 and week 2 vs. 10) corresponding to digit and forelimb release and regrasp. Once again, there was a significant decrease in percent movement across injury severity ($p < 0.05$). The three abnormal movements (Figure 7) characterized by the absence of digit function, are directly proportional to injury severity. There was a significant increase in percent movement across injury severity ($p<0.05$).

**Wrist movement**

The following movements were seen during the experiment: flexion and/or extension of the wrist and rotations inward and/or outward of the wrist. Wrist movement was generally used by the rodent to help position the pasta piece in an orientation that would be conducive to eating.

Wrist movement was affected by injury severity (Figure 8). Although there is no clear pattern, it is evident that wrist movement is completely absent in the severely injured animals until week 10. In mild injuries, wrist movement plays a very small role in pasta manipulation throughout the testing period compared with naive animals. The results show there is a dominant paw for wrist rotation.
Time

The time to eat was also recorded, beginning with the first bite of the pasta and ending when the pasta piece was fully eaten, the halfway point was also recorded. The time to eat the pasta was not sensitive to the effects of SCI. In the vermicelli handling test (Allred, 2008) the time to eat pasta after middle cerebral artery occlusion (MCAO) and Ischemic sensorimotor cortex (SMC) lesions was not significantly changed after the lesion.

What the time showed (Figure 9), in relation to the elbow pasta test, was that there may have been a learning curve when it came to manipulation techniques. For each respective group (naive, mild, and severe), the rats seemed to become more efficient in manipulating the pasta after 10 weeks. Across all injury severities, the time to eat the pasta piece decreased over time. For the most part, the functional deficits of the mild and severe groups did not contribute to an increase in eating times.

Discussion

The purpose of this experiment was to develop a quantitative measure of bimanual normal and abnormal digit, forelimb, and wrist movement. By using elbow pasta and analyzing spontaneous eating, the test is simple and easy to administer. According to Whishaw (1992), limb use during feeding can be divided into two different phases, reaching for and grasping the food and then manipulating the food during the course of eating. The focus of this experiment was on the second phase, bimanual manipulation. We are especially interested in bimanual paw use given the lack of tests for experimental models and the prevalence of bimanual tasks in daily living for both humans and rats. Therefore both
forelimbs were analyzed. There were no significant differences in the amount of movements between the right and left forelimbs and digits. Displaying no paw preference is consistent with rat forelimb behavior (Peterson, 1934; Whishaw, 1992). By looking at how the forelimbs interact as a unit to manipulate the pasta piece, individual movement patterns of normal and abnormal movement were identified and defined. The quantitative measure of these movement patterns proves to be a valid measurement because of its ability to measure both forelimb function and deficits while maintaining sensitivity to all lesion severities.

The elbow pasta test proved valuable in distinguishing movement types. Both the shape and size of the pasta required bimanual manipulation. The Barilla elbow pasta adds an extra twist to the typical elbow macaroni shape. The curved shape and the extra twist forces the rat to not just simply move the pasta to its mouth, but to rotate and turn the pasta into a position suitable for eating. The shape mandates the use of skilled movements/adjustments, and therefore, the test administrator can clearly see when the use of skilled movements are either present or absent. In contrast, paw use during eating of straight pasta, as seen in the Vermicelli Handling Test (Allred, 2008), typically relies on a guiding paw which makes multiple digit adjustments and a stabilization paw which makes relatively few movements. After cervical SCI, we found that the rats made few movements with either paw when eating straight pasta and used the teeth to pull the pasta into the mouth. Thus, the shape of the pasta appears to be an important and necessary feature of sensitivity when assessing forearm and digit function after SCI.
The size of the pasta, which mandated the use of both paws by the rat, did not prove to be a factor in adjustments made. The frequency of adjustments made during the large pasta and small pasta phase were not significantly different.

Both the normal and abnormal movement patterns were sensitive to injury severity. The naive, control group, used normal movements almost exclusively. Comparing the two injury groups to the control group, the severe injury group used normal movements the least while the mild injury group fell in between the two. Normal movements (digit and forelimb release and regrasp, and digit release and regrasp) declined after SCI. The results also show that after a severe SCI, abnormal movements occur at a greater frequency than after a mild SCI, while the naive group showed little use of abnormal movement. Abnormal movements (fail to release or regrasp and forelimb only release and regrasp) increased after SCI. The normal and abnormal forelimb adjustments were fairly stable over the 10 week testing period. Therefore, this test may be sensitive to the permanent loss of motor neurons.

The next step for this study is to verify the lesions and to correlate the loss of motor neurons to the functional deficits between injury severities. The elbow pasta test could be extended to further investigate bilateral motor skill learning. Also, a larger subject pool would be useful in distinguishing more significant differences among the injury severities.

In conclusion, using the elbow pasta handling test would be useful in validating the efficacy of pre-clinical agents and therapy development because the test measures both return of
functions and reduction of deficits of forearm movements, and is sensitive to a broad range of injuries. It also documents persistent deficits in bimanual function which should be the target of future drug and training interventions. Small gains in motor control may result in marked gains in function and the elbow pasta test appears to have properties to detect both normal and abnormal changes in function.

Acknowledgements

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Figure 4. Contusion effects on forelimb function. By distinguishing between normal and abnormal movements, forelimb deficits in injured groups become evident. 

A. Normal movements show a clear decrease as injury severity increases. 
B. Abnormal movement increases as injuring severity increases. The frequency of both normal and abnormal movement remains fairly stable across all time points.
Figure 5. Contusion effects on forelimb function. By separating measures of right and left paw, validates the position of the lesion (centered at C5) since there are no significant differences between the left and right paw measures. It also shows that there does not seem to be a dominant paw used in manipulation of the pasta piece. Keeping the left and right paw measures separate, it is apparent that elbow pasta requires bimanual manipulation. Normal movement in the left paw (A) and right paw (B) decreases as injury severity increases. Abnormal movement in the left paw (C) and right paw (D) increases as injury severity increases.
Figure 6. Normal behavior patterns. **A and B.** Average % movement of digit and forelimb release and regrasp of the left and right paw respectively. Mild, small pasta group had significant differences over time (week 1 vs. 2 and week 2 vs. 10). **C and D.** Average % movement of digit only release and regrasp of the left and right paw respectively. In these two normal movement patterns, which are characterized by digit function, frequency of each movement is inversely proportional to injury severity.
Figure 7. Abnormal movement patterns. A and B. Average % movement of forelimb only release and regrasp of the left and right paw respectively. C and D. Average % movement of failing to release measure of the left and right paw respectively. E and F. Average % movement of failing to regrasp measure of the left and right paw respectively. These three abnormal movements, characterized by the absence of digit function, are directly proportional to injury severity.
Figure 8.  A. The number of left wrist movements per pasta piece was counted. B. The number of right wrist movements per pasta was counted. The right paw seems to have some dominance over the left when it comes to wrist movement (mainly used to facilitate pasta rotation). It is clear that injury severity has a large effect on wrist function. Naïve group wrist movement remains fairly stable across all time points. Mild injury wrist movements appear to be more sporadic, while severe injury wrist movements do not appear until week 10.

Figure 9. The time was not statistically analyzed because there was no conclusive pattern that was sensitive to injury severity. Recording time shows a possible learning curve; the time to eat generally decreased with respect to each individual group (naïve, mild and severe).
Table 2. The number of adjustments per pasta piece. Normal movements include D+F R/R and D only R/R and abnormal movements include F only R/R, fail to release, and fail to regrasp. Total movements include all 5 movement patterns. Values are mean ± standard error mean. Statistical analysis for large and small pasta and right and left paw were kept separate. Normal movement, * significantly less than naive (p<0.05). Abnormal movement, * significantly greater than naive (p<0.05).
References

National Institute of Neurological Disorders and Stroke, 2010


Whishaw IQ, Gorny BP, Pellis SM. Skilled reaching in rats and humans: evidence for parallel development or homology. Behav Brain Res 1992;47:59-70

