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Approximate Entropy Values Demonstrate Impaired Neuromotor Control of Spontaneous Leg Activity in Infants with Myelomeningocele

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2 Approximate Entropy Values Demonstrate Impaired Neuromotor Control of Spontaneous Leg
3 Activity in Infants with Myelomeningocele

4 **ABSTRACT**

5 **Purpose:** One obstacle to providing early intervention to infants with myelomeningocele
6 (MMC) is the challenge of quantifying impaired neuromotor control of movements early in life.

7 **Methods:** We used the nonlinear analysis tool Approximate Entropy (ApEn) to analyze
8 periodicity and complexity of supine spontaneous lower extremity movements of infants with
9 MMC and typical development (TD) at 1, 3, 6 and 9 months of age. **Results:** Movements of
10 infants with MMC were more regular and repeatable (lower ApEn values) than movements of
11 infants with TD indicating less adaptive and flexible movement patterns. For both groups ApEn
12 values decreased with age, and the movements of infants with MMC were less complex than
13 movements of infants with TD. Further, for infants with MMC, lesion level and age of walking
14 onset correlated negatively with ApEn values. **Conclusions:** Our study begins to demonstrate the
15 feasibility of ApEn to identify impaired neuromotor control in infants with MMC.

1 **INTRODUCTION AND PURPOSE**

2 Myelomeningocele (MMC) is the most common neural tube defect in the United States,
3 affecting 1,500 to 2,000 infants born each year ¹. A primary effect of MMC is impaired sensori-
4 motor function of the lower extremities, negatively influencing the ability to walk. The
5 likelihood that children with MMC will walk ranges from approximately 20% for high lumbar
6 lesions to 80% to 90% for sacral lesions, with a mean onset at 3 years or older ^{2,3}. Those who do
7 walk tend to expend a high amount of energy on walking, and by late childhood many shift to
8 wheelchairs for community ambulation ²⁻⁴.

9 Although wheelchair use to save energy for other tasks may be the optimal decision at the
10 time, this solution does not represent the optimal outcome overall. Minimizing gait energy costs
11 and maximizing gait function to allow for independent ambulation across the lifespan would be
12 an ideal outcome. Although this ideal outcome is not universally feasible, recent advances in the
13 study of neuroplasticity and neurorehabilitation suggest that better outcomes are possible.
14 Known principles of experience-dependent neuroplasticity include “use it or lose it”, “use it and
15 improve it”, “specificity”, “repetition, intensity, time, salience and age matter” ⁵. Based on these
16 principles, we propose that early intervention starting at birth, as opposed to our observations
17 here and previously of physical therapy intervention starting around 3, 6 or even 9 months of age
18 ⁶, is necessary to promote optimal sensori-motor development of the lower extremities and future
19 walking ability in infants with MMC.

20 Admittedly, many obstacles exist to providing aggressive early intervention from birth on
21 for infants with MMC. Multiple medical issues may limit the time available for or shift the
22 priority away from therapy interventions concerning long-term goals; parents or caregivers may
23 perceive infants with MMC as fragile; or limited therapist and family resources may make very

1 early intervention difficult to accomplish. Our focus here is on yet another important obstacle:
2 the challenge of quantifying impaired lower extremity function early in life and relating lower
3 extremity control early in infancy to later functional ambulation outcomes.

4 The challenge of quantifying impaired lower extremity function early in life and relating it
5 to later functional ambulation outcomes is multi-factorial. Many of the early motor milestones
6 are based on head and upper extremity movements, and infants with MMC generally do not
7 demonstrate difficulty with these types of movements. They do have difficulty with lower
8 extremity movements, which are generally not documented until later in motor milestone
9 progressions on such measures as the Bayley Scales of Infant Development⁷ or the Test of Infant
10 Motor Performance⁸. Although therapists can use lesion level and assessment of muscle strength
11 as one component of their clinical decision-making process, these assessments are at the body
12 structure and function level of the World Health Organization International Classification of
13 Functioning, Disability and Health (ICF) model⁹ and arguably more removed from the goal of
14 walking than an ICF activity level measure would be. Although many reports show ambulation
15 outcomes are highly related to neurological level, there is still much disparity in outcomes as
16 defined by lesion groups^{10,11} or muscle function¹². Further, manual muscle testing is fairly
17 subjective and unstable in children with MMC under 5 years of age¹³ and motor development
18 preceding ambulation varies even among children with MMC who have similar muscle
19 function¹⁴. There are many factors beyond lesion level that contribute to walking achievement in
20 children with MMC¹². Our argument here is that an objective activity level assessment will
21 provide more accurate and specific information about impairments and change in infant lower
22 extremity function than current body structure and function level assessments. Although it has
23 been demonstrated at an activity level that infants with MMC spontaneously move their lower

1 extremities less than infants with typical development (TD) ^{6,15}, less movement quantity alone is
2 not sufficient to justify or guide therapeutic intervention.

3 In addition to assessing quantity of movements, another possibility is to assess how the
4 movement changes over time. Nonlinear methods of analysis assess qualitative aspects of
5 movement by directly exploring how each point in a movement trajectory influences the next and
6 how movement patterns emerge over time. By showing how the movement trajectory changes
7 across time, nonlinear methods can provide insight into the neuromotor control of the movement.
8 A specific nonlinear tool that can quantify dynamic movement patterns is Approximate Entropy
9 (ApEn). ApEn analyzes the regularity and repeatability of a signal over time. Values at zero
10 signify greatest regularity and absolute rigidity of movement patterns, while values near 2
11 represent great irregularity and very noisy movement patterns. We define these two ends of the
12 spectrum as movement patterns with low complexity, while mid-range values correspond to
13 movements that are highly complex. Thus, complexity is equated with the most well-controlled
14 and adaptive movement patterns^{16,17}.

15 Here we follow the theoretical perspective that health and optimal sensorimotor function is
16 associated with a state of maximum complexity ¹⁷⁻²⁰. We test the hypothesis that spontaneous
17 lower extremity movements of infants with MMC are less complex and less organized than
18 movements of infants with TD, as indicated by lower ApEn values in infants with MMC.
19 Identifying impaired neuromotor control of lower extremity movements in infants with MMC
20 will provide support for early intervention to promote optimal sensori-motor development of the
21 lower extremities and walking ability. Further, this tool may be used to assess change in
22 underlying control due to development or specific interventions.

23 **METHOD**

1 The infants whose data we present here were participants in two different studies of infant
2 stepping in our laboratory, one longitudinal (Study 1) and one cross-sectional (Study 2). Each
3 study included measurement of treadmill stepping responses as well as separate recording of
4 supine spontaneous leg movements. Although the treadmill stepping protocols were different
5 between the studies, the overall length of testing and the amount of activity the infants performed
6 was similar.

7 For Study 1, infants with MMC and TD came into the laboratory at 1, 3, 6, 9 and 12
8 months of age and again at walking onset. We used a 6-camera Vicon Peak Motus real-time
9 system (Vicon Motion Systems, Centennial, CO) to collect reflective marker position data at 60
10 Hz during treadmill stepping and spontaneous movement testing^{6,21}. For Study 2, only infants
11 with MMC participated and were between the ages of 2-5 months or 7-10 months. We used 2
12 synchronized digital camcorders filming at 60Hz to record reflective marker positions during
13 treadmill stepping and spontaneous movement testing²². An additional 12 infants with TD were
14 invited to participate to increase our sample size and match the ages of the infants with MMC in
15 Study 2. We previously published data on the quantity of spontaneous movements for a subset of
16 the infants from Study 1⁶. Here we have expanded our sample to include additional, older
17 infants, and use a nonlinear analysis of complexity of lower extremity spontaneous movements
18 to look more closely at development of segmental control.

19 **Participants**

20 Overall, we included the data points for 56 infants in our analyses. Infants were 1 month of
21 age (MMC = 5, TD = 9), 3 months of age (MMC = 8, TD = 9), 6 months of age (MMC = 7, TD
22 = 6) or 9 months of age (MMC = 6, TD = 6). The data were a mix of cross-sectional and
23 longitudinal; about half of the infants were tested more than once as they reached the older age

1 groups. Specifically, two infants with MMC were tested at all 4 time points, 3 were tested 3
2 times, 3 were tested 2 times and 3 were tested once. Ten infants with TD were tested twice and
3 10 were tested once. Infants with TD were without known cognitive, sensory or motor
4 impairments. Infants with MMC had lesions (level of repair) at or caudal to L1, and were
5 excluded if they had neuromotor abnormalities other than those associated with MMC (e.g.
6 Arnold Chiari II, hydrocephalus) or if they had a gestational age at birth < 28 weeks. We
7 recruited infants through fliers and MMC clinics in hospitals [REDACTED]
8 [REDACTED]. Approval for the study was granted through the Institutional Review Board at
9 the [REDACTED] and parents provided written informed consent for their infants to
10 participate in this study. Tables 1 and 2 contain participant characteristics.

11 **Data Collection**

12 For all spontaneous movement testing, we removed clothing and diapers and attached
13 reflective markers (8mm diameter) to the lateral surface of the greater trochanter, ventral surface
14 of the patella and ventral surface of the third metatarsal. We placed infants supine on a towel-
15 covered firm surface. We held their legs extended and parallel for the initial 10 s of each trial,
16 then released their legs for the duration of data collection. A spotter stood near the infants' head
17 and maintained a hand on each shoulder to prevent the infant from rolling or scooting. Infants
18 remained in supine and moved their legs freely. During trials, parents and researchers maintained
19 conversation but did not directly interact with the infant. For Study 1, bilateral lower extremity
20 reflective marker data were collected for 2 2-minute trials and 1 1-minute trial. For Study 2, we
21 collected data from the right leg for 2 minutes and then from the left leg for 2 minutes. Infants
22 were picked up and held by their parent between trials.

23 For infants with MMC, we recorded aspects of the infant's medical history including lesion

1 level, surgeries and musculoskeletal conditions. We noted if one leg was more affected than the
2 other. If the legs were equally affected, and for infants with TD, we assigned the right leg as less
3 affected for statistical analysis. For all infants, we took anthropometric measurements including
4 body length, weight, greater trochanter to lateral malleolus length, thigh length, foot length, thigh
5 circumference and leg circumference. We assessed concurrent motor skill development level by
6 administering the motor items from the Bayley Scales of Infant Development II ⁷. We recorded
7 the date of administration and whether the infant was able to perform the skill on this day.

8 **Data Analysis**

9 Study 1 data were collected directly in the Vicon Peak Motus software program. Study 2
10 data were transferred from the digital cameras into the software and synchronized. We then
11 digitized hip, knee and foot markers for each trial. We were able to successfully identify the
12 markers for the first 6147 frames of every trial, corresponding to the first 102.5 seconds of data
13 from each 120-s, 60 Hz recording session. Using the same number of data points for every trial is
14 important for calculating ApEn, so longer trials were shortened to provide a consistent amount of
15 data for every trial. We calculated hip segmental angles as the angle between the thigh segment
16 and the surface on which the infants rested. The angle data were then filtered with a 6 Hz
17 Butterworth filter and exported for further analyses.

18 Before we could use the nonlinear tool ApEn to assess the complexity of infants'
19 spontaneous movement data we first had to test the hip angle data for a deterministic structure
20 (mathematically defined as non-random). We used Chaos Data Analyzer (CDA) software
21 Professional Version²³ to create randomly shuffled surrogate datasets for all hip angle time
22 series^{24,25}. Subsequently, we computed the largest Lyapunov Exponent values for all surrogate
23 and original time series and compared them. Significant differences were found between the

1 surrogate and original Lyapunov Exponent values, indicating that the original hip angle data
2 were not random, but deterministic.

3 Next we used MATLAB programs to determine the parameters necessary for ApEn
4 calculations ($m = 2$ and $r = 0.2$) and then to calculate ApEn. Note that determining parameters m
5 and r involve numerous calculations more detailed than elaborated here. For in-depth description
6 of the process, readers are directed to Stergiou et al., 2004²⁵. To calculate quantity of
7 movements, we tested our data to find a threshold for movement identification that was
8 consistent with our observations of spontaneous movements during frame-by-frame video
9 analysis. We wanted to define a threshold that was much more sensitive to small movements
10 than a trained observer could see, while still consistent with observed amounts of movement. We
11 defined a movement as more than 2 degrees of hip flexion or extension in the sagittal plane in
12 167 ms, and counted the number of times this threshold was exceeded per trial. A lower number
13 for the quantity of movement value indicates fewer and/or shorter movements.

14 **Statistics**

15 We used a 2 (group: MMC or TD) x 2 (leg: more or less affected) x 4 (age: 1, 3, 6 or 9
16 months) linear mixed model to test for main effects and interactions. Dependent variables were
17 ApEn values in the first test and quantity of movement in the second. Group, leg and age were
18 treated as fixed effects with participant as a repeated measure (by age and leg) with a diagonal
19 structure. To look at relationships between ApEn values, motor development and factors
20 affecting motor development in infants with MMC, we tested for Pearson correlations between
21 ApEn values and lesion level (high = L1, L2, medium = L2/L3, L3, L4, or low = L4/L5, L5, S1),
22 ponderal index and age at which we observed the infant demonstrate selected items of the Bayley
23 scale (as shown in Table 3). We chose five items to represent major milestones across the age

1 range of our study: sits alone momentarily, sits alone 30 seconds or more, pulls to standing
2 position, walks with minimal help and walks alone, 3 steps or more. We used a two-tailed
3 Pearson correlation to determine if ApEn values were significantly correlated with the selected
4 variables in infants with MMC. For the significantly correlated milestones, we used a one-tailed
5 correlation to follow up and test whether ApEn values at 1, 3, 6 or 9 months of age were
6 significantly correlated with the age at which we observed achievement of the selected
7 milestone. We did not test for correlations in infants with TD because we only had complete
8 Bayley items for 14/30 infants with TD as we did not follow the infants with TD in Study 2 after
9 their 9-month visit to find out when they started walking independently. We used Predictive
10 Analytics Software (SPSS: An IBM Company, Chicago, IL) version 18 for statistical analysis
11 and set our alpha level of significance at 0.05.

12 **RESULTS**

13 **ApEn Values**

14 For the ApEn linear mixed model, we obtained a significant group effect ($F[1,80]= 6.40$,
15 $p = 0.01$). There was not a significant leg effect or age effect. There were no significant
16 interactions. As shown in Figure 1, infants with MMC demonstrated lower ApEn values than
17 infants with TD.

18 **Quantity of Movement**

19
20 For the quantity of movement linear mixed model, we obtained a significant group effect
21 ($F[1,89]= 24.95$, $p < 0.01$) and age effect ($F[3,44]= 5.73$, $p < 0.01$). There was not a significant
22 leg effect or any significant interactions. As demonstrated in Figure 2, the significant group
23 effect was due to infants with MMC producing fewer movements than infants with TD. For the
24 significant age effect, infants produced fewer movements as they got older. Follow-up analysis

1 revealed that infants produced fewer movements at 6 and 9 months of age as compared to 1
2 month of age (p 's < 0.05).

3 **Correlations**

4 For infants with MMC, there was a significant two-tailed negative correlation between
5 ApEn values and the age at which we observed walking alone, 3 steps or more (-0.48, $p = 0.02$).
6 We followed up with one-tailed correlations between the age at which we observed walking
7 alone, 3 steps or more, and ApEn values at 1 month (*NS*), 3 months (-0.82, $p = 0.02$), 6 months (-
8 0.86, $p = 0.01$) and 9 months (-0.79, $p = 0.03$). Lower ApEn values for infants with MMC at 3, 6
9 and 9 months of age were significantly correlated with later age of walking alone, 3 independent
10 steps. There was also a significant one-tailed negative correlation between ApEn values and
11 lesion level, higher lesion levels were correlated with lower ApEn values (-0.30, $p = 0.02$).
12 Correlations between ApEn values and other motor milestones or ponderal index were not
13 significant.

14 **DISCUSSION**

15 The infants with MMC in our study demonstrated lower overall ApEn values than infants
16 with TD from primarily cross-sectional measurements at 1, 3, 6 and 9 months of age. Lower
17 ApEn values for infants with MMC represent less complex and thus less organized lower
18 extremity movements as compared to their peers with TD. Less organized movements have also
19 been observed in the spontaneous upper extremity movements of infants with brain injury²⁶ and
20 postural control in infants born preterm²⁷. Less organized movements reflect impaired
21 neuromotor control of movement and ApEn values are a sensitive tool for therapists and
22 researchers to use to quantify neuromotor control of movement and show improvement as a
23 result of intervention.

1 Although the patterns of results for quantity of movement and ApEn values show similar
2 trajectories, ApEn measures aspects of movement beyond mere quantity. This is demonstrated in
3 the 3-month data points, where the group difference in ApEn values (Figure 1) is smaller than
4 the group difference in quantity of movement (Figure 2). If ApEn values were purely reflective
5 of quantity of movement, we would expect to see identical trajectories for ApEn and quantity of
6 movement. Future studies are necessary to see if ApEn measures are more sensitive than current
7 measures to changes in neuromotor control of spontaneous lower extremity movements with
8 intervention, however previous research suggests it might be ^{27,28}.

9 Beyond quantity of movement, ApEn values reflect the regularity and repeatability of the
10 movement patterns exploring how similar different time points are during the movement,
11 providing a measure of overall complexity. ApEn values exist on a continuum of 0 to 2. An
12 ApEn value of 0 represents complete regularity of a pattern and is a low complexity state. An
13 ApEn value of 2 represents complete irregularity of a pattern and is also a low complexity state.
14 A high complexity state is somewhere in the middle of the range. Our results showed ApEn
15 mean values for all infants ranging from approximately 0.13 to 0.25, indicating that spontaneous
16 leg movements were closer to the regular pattern end of the continuum compared to other types
17 of movement, which makes sense based on the inherent oscillatory nature of leg movements.
18 Studies of supine and sitting postural control in infants found ApEn values of around 1 and 0.23-
19 0.63, respectively, more in the middle of the continuum^{27,28}. Additionally, infants with MMC in
20 our study produced leg movements with lower ApEn values than their peers with TD, indicating
21 more regularity and less complexity across their kicking movements, consistent with impaired
22 neuromotor control.

1 An important point to consider is that both groups have higher ApEn values at one month
2 than at nine months. In general ApEn values are decreasing with age, indicating more regularity
3 and less complexity in kicking movements across time. One could take the values out of context
4 and interpret that MMC one-month ApEn values being approximately equal to TD nine-month
5 values means infants with MMC are “better” than infants with TD and reach the goal of lower
6 ApEn values faster. This interpretation would not be correct, however, as it overlooks the fact
7 that kicking movements change across time, infants at one month of age do not move their legs
8 like infants at nine months of age. As control develops, infants with TD are able to hold their
9 upper leg stable and move only their lower leg ²⁹. It follows that by moving only one segment,
10 instead of two, movements would become more regular and less complex, leading to lower ApEn
11 values. Additionally, thinking of the emergence through time of more alternating kicks and
12 eventual walking, it also fits that spontaneous leg movements would become more regular and
13 less complex as infants strengthen their patterns of alternating leg movements. Lower ApEn
14 values within age groups for infants with MMC at 3, 6 and 9 months of age, however, were
15 significantly correlated with later age of walking alone, 3 independent steps. This indicates a
16 likely interaction with lesion level, as lower ApEn values were correlated with higher lesion
17 levels. These results imply that neuromotor control of leg movements in infants with MMC is
18 fundamentally different than in infants with TD; we need to design further studies to specifically
19 investigate and understand the factors affecting developmental trajectories in infants with MMC.

20 ApEn values must always be interpreted in context; for spontaneous leg movements
21 infants with TD show a pattern of decreasing values across time as neuromotor control develops
22 and movement patterns change. Although lower ApEn values appear ideal for infants with TD,
23 this does not appear to be the case for infants with MMC. Infants with MMC start off with lower

1 ApEn values as compared to their peers with TD and decrease further over time, and those with
2 the lowest values achieve independent walking later. ApEn values for infants with MMC are
3 following the same trajectory as infants with TD, however they have consistently lower ApEn
4 values than their peers with TD at comparable ages. This difference is important as it reflects a
5 unique characteristic of dynamic control between groups in neuromotor control and/or
6 movement patterns of spontaneous leg movements at comparable age and experience levels.

7 Currently, although they may be evaluated before discharge from the hospital following
8 birth, physical therapy intervention to address impaired neuromotor control for infants with
9 MMC is typically initiated around 3, 6 or even 9 months of age ⁶ (see Table 2). This is in contrast
10 to adults with spinal cord injury, for whom therapists, researchers and third-party payers
11 recognize the importance of aggressive early intervention to promote positive neural plasticity
12 changes and recovery of function. Adults with spinal cord injury start physical therapy as soon as
13 possible, with aggressive therapy initiated when they are medically stable, within days or weeks
14 of their injury. Infants with MMC, however, are approximately 11-17 months post lesion when
15 therapy is initiated. This approach accepts a loss of plasticity and does not promote the
16 development of optimal neuromotor control.

17 What happens across the first months of life, before therapy is typically initiated, is of
18 crucial importance to the development of optimal neuromotor control. Although infants with
19 MMC demonstrate the same quantity of spontaneous kicking movements before and at birth,
20 they demonstrate less movement from one month of age on as compared to infants with TD
21 ^{6,15,30-32}. Lower quantity of movement relates to less organized movement through less repetitions
22 of the perception-action cycle. A lower number of movements provide diminished opportunities
23 to develop coordinated movements and neural networks that support stable leg movement

1 patterns³³. Infants with MMC do respond adaptively to external constraints by increasing or
2 decreasing quantity of kicking¹⁵, demonstrating that their lower quantity of movements is
3 amenable to intervention. We propose that increasing the quantity of lower extremity movements
4 and cycles of perception-action from birth on should lead to optimal neuromotor control of the
5 legs, and that this will be reflected in higher ApEn values in infants with MMC indicating more
6 organized movements and better clinical outcomes.

7 It could be argued that lesser movement quantity alone is a sufficient, easier to obtain
8 measure of neuromotor delay in infants with MMC. Barriers to using movement quantity as a
9 clinical assessment, however, include standardizing the definition of a movement, introducing
10 observer-related variability and addressing the natural variability in infant performance. For
11 these reasons, it would be very difficult for an observer to use a stopwatch and get reliable
12 measurements of quantity of spontaneous leg movements. One could use cameras and software
13 analysis, as we do in the laboratory. While this increases the reliability of the assessment it
14 makes it much less “clinic friendly”. ApEn, alternatively, can measure the regularity and
15 complexity of movement patterns as long as some minimal amount of leg movement is recorded.
16 Repeated measurements could theoretically be used to assess changes in the regularity and
17 complexity of spontaneous kicking patterns across time, independent of the fact that an infant
18 kicked more or less at a given session. We did not, however, test the inherent variability of
19 repeated measurements in this study.

20 In summary, we have shown here that ApEn reflects impaired neuromotor control and
21 less organized, less complex movements of the lower extremities of infants with MMC as
22 compared to infants with TD starting at one month of age. Our study begins to demonstrate the
23 feasibility of ApEn as a valuable tool for identifying and quantifying impaired neuromotor

1 control in infants with MMC. ApEn assessment adds unique information to current clinical
2 assessments and supports the need for therapeutic intervention early in life.

3
4 **STUDY LIMITATIONS**

5
6 The major limitation of our study is that it is not a longitudinal design. Additionally, we
7 report only lesion level of surgical repair, which is not as meaningful for behavior as a functional
8 neurological level. We only tested infants once at each time point, and infant behavior is
9 inherently variable. It would be ideal to test infants twice at each age and follow them from birth
10 through independent walking, and we plan to pursue such a study. Such a design would allow us
11 to test the inherent variability of ApEn measurements as well as rigorously test the relationship
12 between ApEn, factors affecting motor development and outcomes in infants with MMC. This
13 study, however, provides necessary background information on the feasibility and usefulness of
14 ApEn as an outcome measure before recruiting infants and their families for a study design that
15 would be much more demanding of their time. We also appreciate the need for software
16 development to allow clinicians to collect and analyze data without using research laboratory
17 resources.

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5

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1 **FIGURE LEGENDS**

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3 **Figure 1.** Mean Approximate Entropy values for each group by age. Error bars represent
4 standard error of the mean. The overall group main effect is significant. TD = typical
5 development, MMC = myelomeningocele.

6

7 **Figure 2.** Mean quantity of movement (defined as greater than 2 degrees of hip flexion or
8 extension in 167 ms) per 6147 frames per trial for each group by age. A lower value indicates
9 fewer and/or shorter movements. Error bars are the standard error of the mean. The overall group
10 and age main effects are significant. TD = typical development, MMC = myelomeningocele.

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