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Upper extremity 3D reachable workspace analysis in dystrophinopathy using Kinect

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Abstract

Introduction—An innovative upper extremity 3D reachable workspace outcome measure acquired using Kinect sensor is applied towards Duchenne/Becker muscular dystrophy (DMD/BMD). The validity, sensitivity, and clinical meaningfulness of the novel outcome is examined.

Methods—Upper extremity function assessment (Brooke scale, NeuroQOL questionnaire) and Kinect-based reachable workspace analyses were conducted in 43 individuals with dystrophinopathy (30-DMD, 13-BMD; ages 7–60) and 46 controls (ages 6–68).

Results—The reachable workspace measure reliably captured a wide-range of upper extremity impairments encountered in both pediatric and adult, as well as ambulatory and non-ambulatory individuals with dystrophinopathy. Reduced reachable workspaces were noted for the dystrophinopathy cohort compared to controls, and they correlated with Brooke grades. Additionally, progressive reduction in reachable workspace directly correlated with worsening ability to perform activities of daily living, as self-reported on the NeuroQOL.

Discussion—This study demonstrates the utility and potential of the novel sensor-acquired reachable workspace outcome measure in dystrophinopathy.

INTRODUCTION

Recent advances in sensor technology, computer science, and engineering have opened the possibility to infuse novel ideas into the clinical outcomes development field. These measures for the most part have relied on time- and effort-intensive methods, which are often dependent on traditional manual tools. An urgent need for innovative upper extremity clinical assessment tools and outcome measures is particularly relevant in Duchenne and

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Becker muscular dystrophy (DMD/BMD), where novel therapeutics are being evaluated for treatment efficacy.

DMD is a progressive, X-linked recessively inherited muscle disorder with an approximate prevalence of 1 per 3,500–5,000 males, making it the most common form of childhood muscular dystrophy (1,2,3). DMD and BMD represent a spectrum of dystrophinopathy phenotypes, a group of muscle disorders resulting from mutations in the *dystrophin* gene at locus Xp21 (4). Different mutations can result in either complete absence or marked deficiency of the dystrophin protein (5,6,7), with a wide spectrum of phenotypes ranging from mild (BMD) to severe (DMD) (8,9). Overall, there is a stereotypical progression of weakness affecting the proximal muscles first, while sparing the distal limb muscles until much later in the course of the disease. For DMD, boys in early childhood (~age 5 years) typically develop hip and shoulder girdle muscle weakness with loss of ambulation occurring between ages 7–12 years, progressing later to involve hand function, and death in early adulthood (10,11). For BMD, the stereotypical pattern of proximal muscle weakness is similar to DMD, but onset of symptoms is later (~age 12 years) with slower progression, and loss of ambulation occurring in adolescence or later, with death usually in late adulthood (12). Therefore, a wide spectrum of disease severity and upper extremity impairment are present across the lifespan in pediatric and adult populations, as well as in ambulatory and non-ambulatory individuals.

In the past decade, there have been tremendous advances in development of promising therapeutic strategies for dystrophinopathy (13,14,15,16). However, such development has also highlighted an urgent need to identify appropriate clinical outcome measures and tools that can evaluate effectively the efficacy of these promising strategies (17,18). Many traditional physical function assessment tools and types of outcome measures are available in the neuromuscular field including: range of motion assessment (ROM), manual and quantitative muscle strength tests (19), functional scales (Brooke) (20,21), timed-performance tests (9-hole peg test, 6-minute walk test) (22,23), motor-performance tests (24,25,26), and patient-reported outcome measures (27,28). In addition, technology-based outcome measure systems are now also being explored (29,30). However, a recent critical review of available upper extremity functional assessment tools and outcome measures found only a few to be suitable for clinical trials and reinforced the need for more innovation in the field (31).

Additionally, expert panels and leading researchers have identified crucial deficiencies in the design and conduct of clinical trials pertaining to muscular dystrophies (32,33,34). One major factor impacting drug development in the dystrophinopathy field is that most of the studies thus far have focused on lower extremity and ambulatory outcome measures as primary endpoints (35,36,37,38,39,40). By limiting studies to ambulatory outcome measures, a significant portion of the population who are non-ambulant are excluded from the opportunity to participate. Furthermore, focusing only on ambulatory outcome measure fails to address issues of critical importance to older individuals across the lifespan, such as impaired upper extremity function, its impact on activities of daily living (ADLs such as feeding, grooming, dressing and bowel/bladder care) and quality of life (41). Other recognized gaps are a lack of objective measures that are sufficiently sensitive to changes in

disease course and available outcomes that can bridge the transition from independent ambulation to wheelchair use. Finally, a major barrier also includes limited data that directly link outcome measures to patient-reported function (32,33,34) as consumers, researchers, regulatory agencies, and pharmaceutical industry have begun to increasingly recognize and appreciate the importance of patient-reported outcome (PRO) measures in determination of clinically-meaningful outcomes and validation of surrogate endpoints for therapeutic trials (42,43,44).

The complex biomechanics of the upper extremity and shoulder joint with its multiple degrees of freedom in movement is challenging to characterize (45,46,47). Yet, fundamentally the primary purpose of the upper extremity is to perform a wide range of daily activities, to position the hand in an optimal location, and to extend reachability to grasp, manipulate, or otherwise interact with various objects and the environment (48,49). Therefore, the concept of reachable workspace, which is well-established in the engineering fields for analysis of mechanical systems such as robots, can serve as the foundation for an intuitive and pragmatic solution to assess overall upper extremity function. The rationale and framework for developing such a region-specific global upper extremity functional outcome measure have been outlined by researchers of upper extremity disability (50,51). Based on kinetic chain theory from kinesiology, which supports the assessment of upper extremity dysfunction on the basis of a whole extremity, a standardized region-specific measure would allow comparison of disability using a common metric across multiple upper extremity disorders.

In an effort to address these complex challenges, we have formed a multi-disciplinary group of investigators to develop an intuitive 3D reachable workspace outcome measure system using a single depth-ranging camera as an alternative to the costly traditional multi-camera motion capture system (52,53). A markerless and contactless sensor-based system with analysis and visualization software has been developed to unobtrusively measure upper limb motion and instantaneously reconstruct an individual's frontal hemi-sphere reachable workspace envelope surface area as a surrogate marker of global upper extremity function (54,55). A proof-of-concept and initial evaluations of the system using an affordable commercially-available single sensor system (Kinect, Microsoft Corp., Redmond WA, USA) have demonstrated validity against a full-scale, sub-millimeter motion capture system (correlation coefficient R=0.89) with accuracy of ±50 mm in hand motion trajectories, high test/re-test reliability (R=0.86–0.93), and promising potential applicability towards neuromuscular disorders (54,55).

In this study, our goal was to demonstrate the application and validity of this system in a group of pediatric and adult individuals with dystrophinopathy. We also aimed to determine the sensitivity of the developed outcomes system to detect change by evaluating the differential effects of a simple loading protocol (500- and 1000-gram wrist weights) on reachable workspace. Finally, we wanted to assess whether the sensor-acquired and automated reachable workspace outcome measure correlates with a validated upper extremity function PRO to provide clinical meaning and relevancy to this novel outcome measure.

MATERIALS AND METHODS

Study Participants

A total of 43 boys and adult men with dystrophinopathy and 46 healthy controls participated in the study. Of the 43 participants with dystrophinopathy, 40 had confirmed genetic analysis showing mutations of the *dystrophin* gene. The remaining 3 participants were diagnosed with dystrophinopathy based on muscle biopsy showing either absent or decreased dystrophin expression and correlative clinical presentation. Healthy control subjects were recruited from the surrounding areas. Demographic and anthropometric information were obtained from each subject. Arm lengths (upper arm + forearm) for each subject were measured directly and extracted automatically from the Kinect sensor collected skeleton data as described previously (54). The Brooke upper extremity functional scale (20) was used to characterize upper extremity function impairments in all subjects. The study protocol was approved by the University Institutional Review Board (IRB) for human research.

Upper Extremity Reachable Workspace Protocol

The experimental protocol for sensor system setup and arm movement detection followed the previously published protocol (54). Briefly, subjects were seated in front of the Microsoft Kinect sensor and underwent a standardized upper extremity movement protocol under the supervision of a study clinical evaluator as described previously (Video S1, available online). A simple set of standardized movements consisted of lifting the arm from the resting position to above the head while keeping the elbow extended, performing the same movement in vertical planes at approximately 0, 45, 90, and 135 degrees. The second set of movements consisted of horizontal sweeps at the level of the umbilicus and shoulder. The protocolized movements for reachable workspace typically took about 1 minute. To standardize the assessment, participants followed the pre-recorded instructor's movement through video feedback. Subjects were instructed to reach as far as they could in the respective directions while keeping the elbow extended without leaning forward or twisting their body (without the use of compensatory movements). When necessary, the clinical evaluator also demonstrated the movements in front of the subject to dictate the speed, to monitor for excessive compensatory movements (trunk rotation or leaning forward), and to further reinforce the order of movement sequence. If the subject leaned or trunk rotations were observed, the recording was repeated from the beginning with adequate rest breaks.

Reachable Workspace Surface Envelope Analysis

The Kinect-tracked 3D hand trajectory was transformed into a body-centric coordinate system, and each individual's reachable workspace envelope was reconstructed in a graphical output using methods described previously (54). The reachable workspace envelope on each side was further divided into 4 quadrants with the shoulder joint serving as the origin. The absolute total and quadrant reachable workspace surface envelope area (m^2) were calculated and normalized by each individual's Kinect-extracted arm length and unit hemi-sphere. This relative surface area (RSA), representing the portion of a unit hemi-sphere, is determined by dividing the absolute reachable workspace area by the factor $4\pi r^2 \times$

(1/2), where *r* represents the arm length (upper arm + forearm). This provides normalization of the data by each person's arm length to allow comparison between subjects.

Patient Reported Outcome (PRO)

To better understand the clinical meaningfulness of reachable workspace, we examined the correlation between the mean total RSAs and the self-reported responses on the "Upper extremity, Fine motor, and Activities of daily living (ADL)" item bank of 20 questions from the NeuroQOL (Neurological Disorders Quality of Life) questionnaire (29,56,57,58). Thirty subjects with DMD completed the NeuroQOL, a psychometrically robust quality of life assessment tool for adults and children with neurologic disorders.

Statistical Analyses

Statistical analyses were conducted using SAS 9.4 software. Data was checked for normality through the Shapiro-Wilk test and analyzed parametrically. Pearson and Spearman correlations were used to determine associations of parametric data and non-parametric data, respectively. Least square regression methodology was used to assess whether associations differed significantly from 0. Student *t*-tests were used to assess differences between 2 groups. ANOVA was used to assess differences between multiple groups, and a *post-hoc* Tukey test was used to determine sub-group differences. Receiver operator characteristic (ROC) analyses were used to determine the criterion cut-off value, AUC, sensitivity, and specificity. For all statistical analyses, a minimum *P*-value of 0.05 was accepted as the level of statistical significance.

RESULTS

Study participants

Basic demographics and description of the dystrophinopathy (n=43) and healthy control (n=46) cohorts by age, height, arm lengths, ambulatory status, and Brooke upper extremity function grade (20) are shown in Supplemental Table S1 (available online). Of the 43 participants with dystrophinopathy, 30 subjects were diagnosed with DMD (average age: 11.7 ± 3.1 years, range 7–21 years) and 13 subjects were diagnosed with BMD (average age: 39.0 ± 16.3 years, range 13–60 years). The healthy control cohort was comprised of 46 boys/ adult men (average age: 27.08 ± 18.07 years, range: 6–68 years). Thirteen of the DMD and 2 of the BMD participants were non-ambulatory at the time of testing.

Arm length measurements in the healthy control and dystrophinopathy cohorts

The clinical evaluator-measured and Kinect-measured arm lengths (upper arm + forearm) for all study subjects are shown in Supplemental Table S1. The control cohort's evaluator-measured and Kinect-acquired mean arm lengths were 58.9cm $\pm$ 9.0cm and 56.1cm $\pm$ 6.6cm, respectively. The dystrophinopathy cohort's evaluator-measured and Kinect-acquired mean arm lengths were 52.7cm $\pm$ 9.5cm and 50.5cm $\pm$ 7.7cm, respectively. The correlation between the evaluator-measured arm lengths and Kinect-acquired arm lengths for control (R=0.959) and dystrophinopathy (R=0.953) cohorts is shown in Figure 1.

Graphical representations of reachable workspace in DMD, BMD, and Controls

Reachable workspace was divided into 4 quadrants with the shoulder joint serving as the origin. The sagittal plane through the shoulder joint defined the ipsilateral and contralateral sides of the workspace relative to the side undergoing assessment, while the horizontal plane at the level of the shoulder joint defined the top and bottom parts of the workspace quadrants (Fig. 2A). Representative graphical illustrations of reachable workspace in DMD subjects (Brooke grade 1–5) and a young healthy control boy (7 years old) are shown (Fig. 2B). Example output graphics of reachable workspace in BMD subjects (Brooke grade 1–3) are also shown (Fig. 2C).

Effect of height and age on reachable workspace relative surface area (RSA)

As described previously, the absolute reachable workspace surface area (m^2) was normalized by each individual's Kinect-measured arm length for calculating the RSAs and to allow for comparison between subjects (54). To assess whether the reachable workspace normalization technique using each individual's arm length is appropriate, age- and height-effects on the RSA were examined. There were no significant correlations between the mean total reachable workspace RSA and age, as well as the mean total RSA and height in the control group. The total RSA was significantly and negatively correlated with both age and height in the DMD subjects ($RSA\_TOT_{DMD} = -0.075*age + 1.47$, p<0.0001; $RSA\_TOT_{DMD} = -0.015*height + 2.68$, P<0.0001) while in the BMD group, total RSA was associated negatively only with age ($RSA\_TOT_{BMD} = -0.005*age + 0.83$, P=0.046; Table 1).

Reachable workspace comparison between healthy controls and individuals with DMD/BMD

The mean RSA of the reachable workspace envelope for all the cohorts (DMD, BMD, control) are shown in both quadrant and total area reachable workspace plot format (Fig. 3A-C; corresponding data in Table 2). An analysis of variance (ANOVA) evaluation with Tukey *post-hoc* analysis revealed significantly reduced RSA of all quadrants for the DMD cohort as compared to the control group (Fig. 3A). The RSA of the BMD group was significantly smaller than the RSA of the control cohort in quadrant 1 and the total RSA (Fig. 3B). There was no significant difference in the RSA of the BMD and DMD groups in quadrants 1, 2, 3, and total RSA. In quadrant 4, the RSA of the DMD cohort is significantly smaller than the BMD cohort. The reachable workspace plot for the combined dystrophinopathy and control cohorts shows significant difference in all quadrants (Fig. 3C).

Reachable workspace and Hand dominance

We tested for any association between reachable workspace and hand dominance for the dystrophinopathy and control cohorts. There was no significant difference in reachable workspace between dominant and non-dominant sides in any quadrant for all cohorts (data not shown).

Reachable workspace analysis by Brooke grade

An ANOVA analysis revealed that the total reachable workspace RSA is associated with levels of impairment as determined by the Brooke scale ($F_{4,137} = 169.5$; $P<0.0001$). Tukey *post-hoc* comparisons indicate that the total mean reachable workspace RSAs for individuals with a Brooke grade 1 was significantly greater than those with a Brooke grade 2 ($P=0.0022$), which was significantly greater than those with a Brooke grade of 3 ($P=0.0001$), which was significantly greater than those with a Brooke grade of 5 ($P=0.0005$), but it did not differ significantly from those with a Brooke grade of 4. There were no significant differences in the total RSA of individuals with Brooke grades of 4 and 5. Analysis by quadrant showed that those dystrophinopathy subjects with Brooke grade 2 (moderate functional limitations) had significantly reduced RSAs in the upper quadrants 1 and 3 when compared to the cohort with a Brooke grade of 1. Both DMD and BMD individuals with Brooke grade 3 lost a significant amount of their RSA in each quadrant, with quadrant 4 (lower ipsilateral) being the most spared. A reachable workspace plot as well as bar graph for dystrophinopathy subjects as categorized by Brooke grade demonstrates changes in reachable workspace due to worsening upper extremity impairment (Fig. 4A,B; corresponding data are shown in Table 3). There was no significant difference in the mean total RSA of the control group and the mean total RSA of the 25 subjects with dystrophinopathy who had a Brooke grade of 1.

Sensitivity of the reachable workspace/Evaluation with loading protocol

The sensitivity of the system was assessed by examining the effects of different loading conditions (under non-weighted vs. loading condition with a 500- and 1000-gram wrist weight) on reachable workspace (Fig. 5). With a 500-gram loading condition, control and BMD groups showed no decrease in RSA in any quadrants and total RSA, while the DMD cohort showed significant reductions in RSA of quadrants 1, 3, 4, and total RSA (Fig. 6A). One-way ANOVA with Tukey *post-hoc* analysis showed that the DMD cohort RSA with a 500-gram loading condition was significantly different from control RSA in quadrants 1, 3, 4, and total RSA. Of the 43 individuals with dystrophinopathy, there were 11 with Brooke grade 1 who completed the 1000-gram loading protocol. The BMD, DMD, and control cohorts with Brooke grade 1 revealed no significant differences in their mean total RSAs without any wrist weight. With the addition of 500- and 1000-gram loading, the mean total RSA of the DMD cohort decreased in a linear fashion that was significantly different from controls, whose total RSA remained unchanged (Fig. 6B). The BMD cohort demonstrated a slight reduction in mean total RSA with addition of the 500-gram load, which was not significantly different from the control group. However, the 1000-gram wrist weight produced decreased mean total RSA that differs significantly from controls.

Clinical meaningfulness of the reachable workspace and association with patient-reported function

There was a strong association (Spearman $\rho = 0.79$) between self-reported upper extremity functional capability and the mean total RSAs for the 27 DMD subjects who completed the 20-question NeuroQOL questionnaire (Fig. 7A). Evaluation of the association between the mean total RSA and a subset of 8 questions of the NeuroQOL that are more relevant for

proximal upper extremity and shoulder function (e.g., shampoo hair, put on and take off pullover shirt, button shirt, pull on trousers, wash and dry body, close zipper, and use spoon to feed) revealed an even stronger association ($\rho = 0.85$).

Box-and-whiskers plots showing the distribution of the total RSA corresponding to whether individuals are capable of performing the listed ADL tasks with no difficulty, some/little difficulty, much difficulty, or unable are shown (Fig. 7B). DMD subjects with significantly reduced mean total RSAs were unable or had much difficulty, while individuals with a high mean total RSA reported no difficulties performing these upper extremity tasks independently. A weak association was noted between the reachable workspace and upper extremity activities that rely primarily on distal fine motor skills.

An ROC curve was generated to determine the optimal mean total RSA cut-off value to identify those who are able to perform the selected eight proximal upper limb associated tasks independently without any difficulty from those who have some difficulty (Fig. 7C). The ROC curve yielded a criterion of >0.6265 (AUC=0.764, *P*<0.001) with sensitivity of 96.2% and specificity of 59.0%. This cutpoint is represented as a dashed line on Figure 6B; above the line indicates that individuals have a high likelihood of being independent with no difficulty performing the listed proximal upper limb tasks. Another ROC curve was generated to determine the optimal cutpoint to identify those who are unable to perform the proximal upper extremity ADL tasks (Fig. 7D). The ROC curve yielded a criterion of 0.4096 (AUC=0.936, *P*<0.001) with sensitivity of 88.0% and specificity of 95.5% and is represented by a dotted line on Figure 6B; below the line indicates that individuals have a high likelihood of being unable to perform the listed proximal upper limb tasks and is dependent on another person for performance of their ADLs.

DISCUSSION

We previously introduced the conceptual framework and detailed methodology (including mathematical algorithms, parameterizations, and transformations) to acquire upper extremity motion data and reconstruct an individual's 3D reachable workspace using a single markerless motion sensor (Kinect) (54). When evaluated simultaneously against a full-scale motion capture system, the Kinect-acquired reachable workspace was found to be comparatively robust with high test-retest reliability and minimal data loss (54). In this study, we extend the clinical validity, applicability, and translatability of the system and propose the reachable workspace as a new outcome measure to address the critical need for objective and more sensitive upper extremity assessment in dystrophinopathy. In addition, we demonstrate the clinical meaningfulness and usefulness of the novel outcome by correlating it with an individual's self-reported upper extremity function in the context of daily living activities. The new outcome measure provides an intuitive graphical visualization that conveys immediate and content-rich information about an individual's overall upper extremity functional capacity at a glance that has not been available previously.

The concurrent validity of the reachable workspace outcome measure in dystrophinopathy was examined by comparing against the standard Brooke upper extremity function scale

(20). The Kinect-based reachable workspace analysis system could differentiate reliably the individuals who had mild impairment from those with more severe upper extremity impairment as classified by the Brooke scale. However, the study also revealed that in the more functional group of individuals, the traditional Brooke grading with its ordinal scale lacked adequate sensitivity. The reachable workspace method demonstrated that subjects with Brooke grades 2 and 3 have a very high variance in their reachable workspace, highlighting the limitations of the currently used ordinal Brooke scale with its lack of granularity. Furthermore, the Brooke scale's ceiling effect for high-functioning participants was readily observed when differential reachable workspace reductions in response to loading conditions (wrist weights) teased out subtle weakness differences among individuals who were all classified as Brooke grade 1. Thus, important advantages of the reachable workspace outcome measure are its continuous nature, which facilitates parametric statistical analyses, its sensitivity to detect changes over a wider range of physical impairment, and its versatility to be used in combination with loading conditions that can minimize ceiling effect.

These results also show that the system can span the wide range of phenotypes encountered in dystrophinopathy as a disease spectrum from the least affected (Brooke =1) to those severely affected (Brooke = 5) in both pediatric and adult populations. In terms of appropriate age range, a wide-range of ages were able to complete the protocol with minimal data loss (ages 6–68 years). The automated data collection system and protocol is quick (approx. 1 minute for each arm's reachable workspace data capture) and designed with reduced participant burden in mind. Those in wheelchairs remained seated and simply moved up to the Kinect sensor for the assessment. Following pediatric populations through growth, as well as difficulty in comparing phenotypes across lifespan, has been a challenging problem for a disease such as dystrophinopathy. However, the normalization technique for reachable workspace using each individual's arm length may provide a solution to this dilemma. We examined the correlation between reachable workspace RSA, age, and height. As expected, the controls showed that neither height nor age correlated significantly with the mean total RSAs, since the arm-length normalization adjusts appropriately for anthropometric differences and thus makes comparison between individuals at various ages and heights feasible. These are practical yet critical considerations for clinical trial design and are especially relevant for rare diseases, where the available participant pool for study recruitment and retention is limited.

The sensitivity of the system was assessed by determining whether the methodology would detect a difference in the reachable workspace RSA with no load, a small (500-gram), or moderately heavy (1000-gram) load on the wrist. In the healthy controls, wrist weights did not significantly impact the reachable workspace. However in the DMD cohort, addition of even a small amount of weight (500-grams, typical of a small household or office object) significantly reduced the upper quadrant reachability and the total reachable workspace. For individuals with BMD and relatively preserved strength, the 1000-gram load resulted in significantly reduced RSA, separating them from healthy controls. These results illustrate both the stability and sensitivity of the developed reachable workspace system to detect small incremental decline (or improvement) in muscle function. Further sensitivity evaluation of the system to detect changes over time is planned in a longitudinal study. In

addition, the results demonstrate flexibility of the system to be used in combination with various weights or exercise fatigue protocols tailored to delineate specific treatment effect in clinical trials, especially in the higher functioning (Brooke = 1–3) groups who most likely will comprise the target population in the majority of the therapeutic interventions.

Importantly, the study examined the clinical meaningfulness of the reachable workspace outcome by correlation with a validated PRO measure (upper extremity questionnaire of the NeuroQOL, Supplemental Table S2). The study shows that an automated, sensor-acquired objective physical outcome measure is capable of high correlation (ρ =0.79) with a PRO. Further focus on a subset of 8-questions of the NeuroQOL which pertain most to proximal shoulder function (e.g. shampoo hair, take off and put on pullover shirt, use spoon to feed), the reachable workspace outcome measure demonstrated even stronger correlation with the PRO (ρ =0.85). The ROC analyses suggest clinically meaningful cut-off values for reachable workspace RSAs that can identify those subjects likely to be independent with these ADLs (RSA > 0.6265) and those unable to perform them (RSA 0.4096). A important implication for dystrophinopathy clinical trial design based on these results is that, inclusion criteria based solely on Brooke grade may be inadequate, since it appears that target population between Brooke grades 2 and 3 may be the most promising group to demonstrate clinically meaningful efficacy in an intervention trial.

A limitation of this study, as is often the case with research in rare diseases, includes the relatively small sample size. However, compared with previous studies in the dystrophinopathy field (31), the study represents one of the largest to specifically investigate upper extremity outcome measures. A distinct advantage of the system in this regard is its scalability, affordability, and minimal equipment requirements to facilitate multi-site and international investigations. An inherent limitation is that for correlation with functional activities, the reachable workspace analysis assumes adequately preserved hand function and may not be applicable in cases or conditions where distal fine motor control function is limited.

Another issue raised regarding reachable workspace may be the differential contributions by contractures and muscle strength affecting the reachable workspace outcome. However, dystrophinopathy natural history studies indicate significant elbow and shoulder contractures (>15°) are not typically present until well after the transition to wheelchair (>2 years), and they are accompanied by severe strength loss due to disease progression.(59) Practically for therapeutic intervention studies, the likely target population is those at a disease stage with decreasing yet still partly preserved proximal upper extremity function, where significant contractures are not prominent associated features (with enough viable muscle available for therapeutic intervention to affect). In our study population where the majority of the individuals were Brooke grades 1–3, the evaluator-measured actual arm lengths matched well with the Kinect-acquired arm lengths, indicating minimal contracture contribution to reachable workspace, at least in this group of dystrophinopathy subjects with either relatively preserved or moderately impaired proximal muscle function.

The next development direction is towards a cloud-based platform which would connect multiple geographically-distributed study sites and allow remote data collection from the

home environment via an internet connected-sensor. Another powerful feature of this technology is its capability to store a complete set of raw digitalized measurements, including detailed motion parameters and video data that can be accessed later, replayed, and analyzed in an unprecedented way. Instead of just having a list of joint angles or strength measures as the sole outcomes legacy, this tool can store detailed data to essentially reconstruct an individual's motion for analysis and re-analysis at a later time. Moreover, the collected data can facilitate sophisticated and data-driven model building using machine-learning methods. Additional applications for telemedicine and remote real-time evaluation of patients or study participants can be also envisioned (60), which would reduce travel burden, not only for individuals with physical disabilities but potentially also for the rapidly-growing aging population.

CONCLUSIONS

Development of a scalable and sustainable remote measurement platform for upper extremity function will facilitate translational science and promises to be a novel tool for conducting clinical trials by reducing cost and participant burden while improving efficiency through automation. A rationally-designed combination of a region-specific global upper extremity outcome measure, such as the reachable workspace, complemented by targeted disease- or function-specific endpoints, may be optimal for future clinical efficacy trials. This study focused on dystrophinopathy, however, this assessment tool and outcome measure system can also be envisioned for use by a wide-range of researchers and clinicians in various neurological and musculoskeletal conditions affecting the upper extremity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

ABBREVIATIONS

3D	Three-dimensional
ADL	Activities of daily living
ANOVA	Analysis of variance
AUC	Area under curve
BMD	Becker muscular dystrophy
DMD	Duchenne muscular dystrophy

NeuroQOL	Neurological Disorders Quality of Life
PRO	Person-reported outcome
QOL	Quality of life
ROC	Receiver operator characteristic
ROM	Range of motion
RSA	Relative surface area

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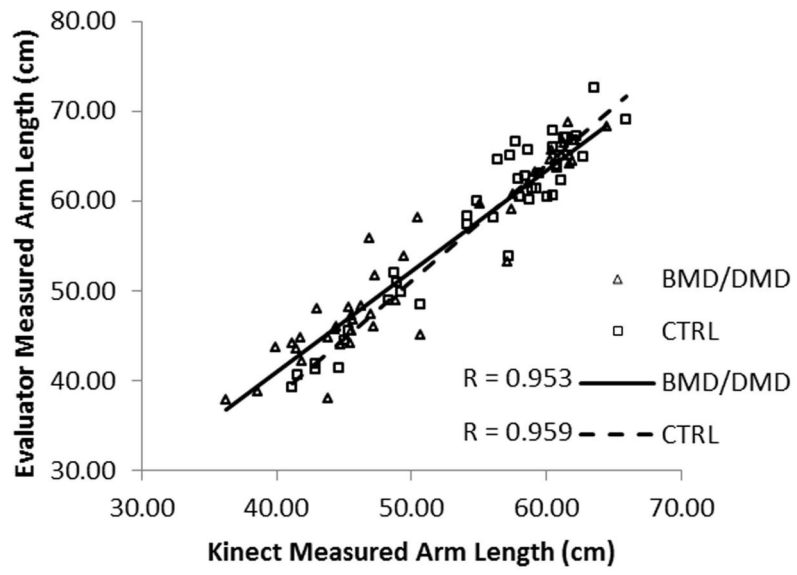
Fig. 1. Correlation of measured arm lengths
Correlation between actual evaluator-measured arm lengths and Kinect-acquired arm lengths for the BMD/DMD and control cohorts.
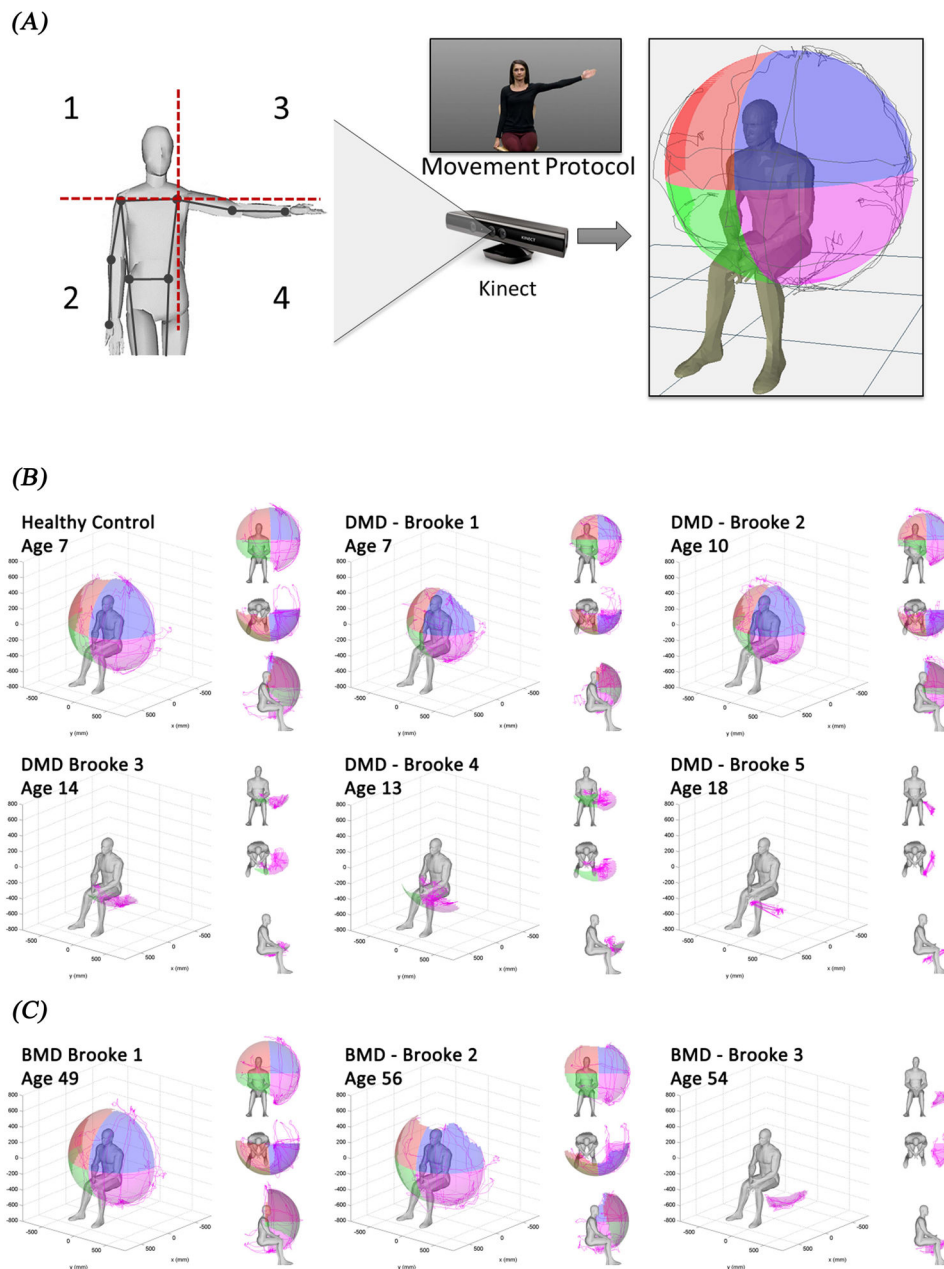
Fig. 2. Intuitive graphical visualization of 3D reachable workspace
(A) Overall schematic of the process to detect an individual's upper extremity motion via Kinect sensor and visualization of the reachable workspace output. The example shows the reachable workspace quadrants as enumerated 1–4 in the left upper extremity perspective. (B) A 7-year old healthy control's reachable workspace viewed from different directions, along with reachable workspaces of individuals with DMD and progressively worsening upper extremity function as classified by Brooke grades 1–5. (C) Reachable workspace from 3 individuals with BMD and Brooke grades 1–3.
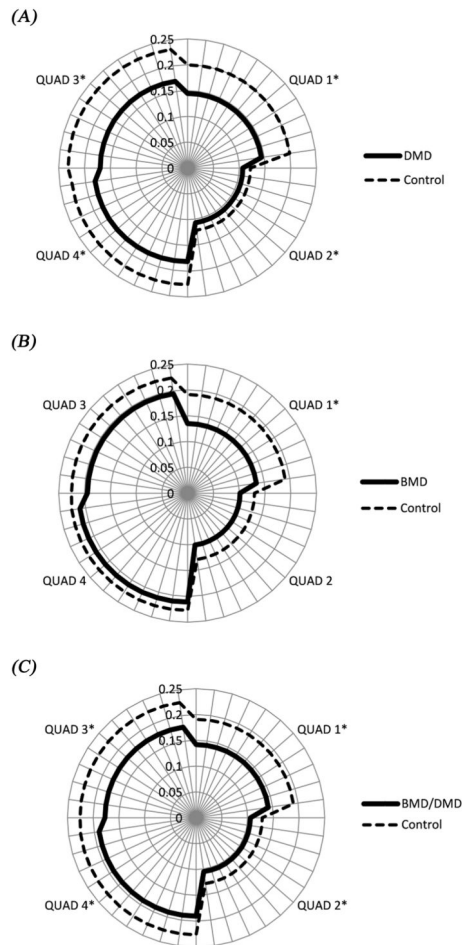
(A)

(B)

(C)

Fig. 3. Difference in reachable workspace between control and dystrophinopathy cohorts
(A) Mean RSAs by quadrant presented in a 2D reachable workspace plot format for the
DMD cohort (solid line) and age-matched control cohort (dashed line); (B) BMD cohort
(solid line) and age-matched control cohort (dashed line), and (C) combined BMD/DMD
cohort (solid line) and all control subjects (dashed line). Plots shown in the right side
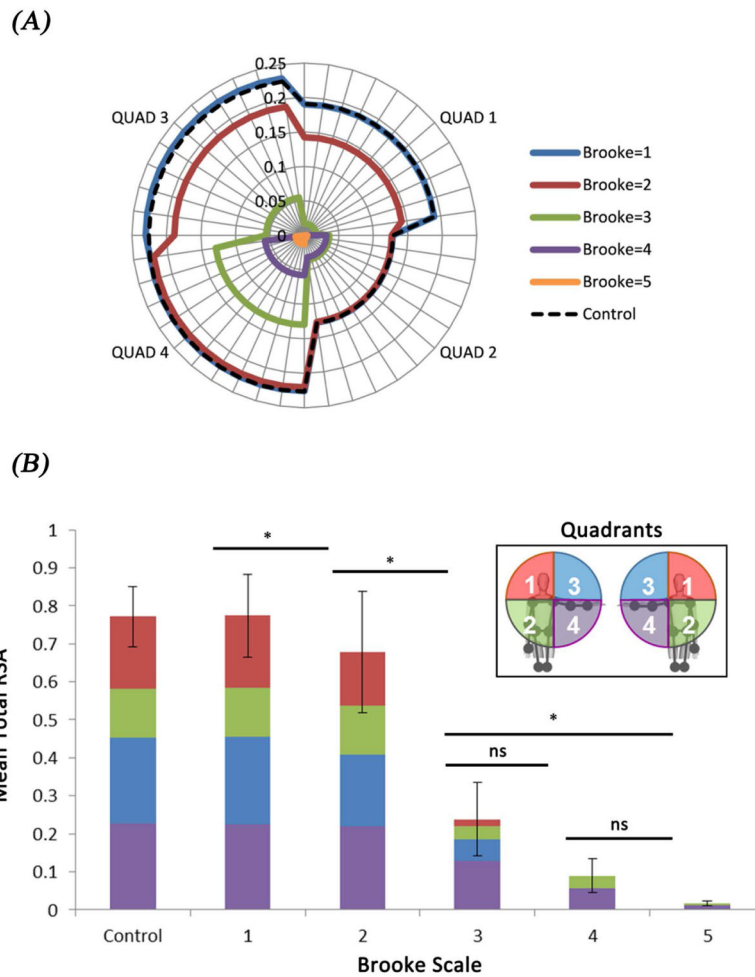perspective (*$P<0.05$).

Fig. 4. Progressive reductions in total and quadrant reachable workspace corresponding to disease severity in dystrophinopathy

(A) Mean reachable workspace RSA by quadrants presented in a reachable workspace plot format, shown in right side perspective. Controls are shown as a dashed line; BMD/DMD patients with Brooke grade 1 are shown with a dark blue line, 2 in red, 3 in green, 4 in purple, and 5 in orange. (B) a bar graph for controls and dystrophinopathy subjects by Brooke grade demonstrating reductions in total and quadrant RSAs corresponding to worsening disease severity as categorized by Brooke grades 1–5 (*$P<0.05$).
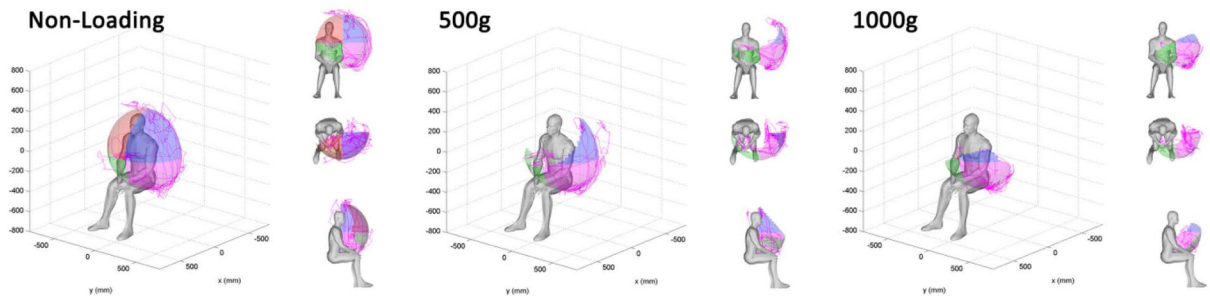
Fig. 5. Reduction in reachable workspace with non-loading vs. loading conditions (500- and 1,000-gram wrist weights)

Progressive change in reachable workspace of an individual with DMD (age 9 years) and Brooke grade 1 demonstrates the sensitivity of the reachable workspace outcome measure to detect incremental changes in upper extremity reachability; shown in left upper extremity perspective.
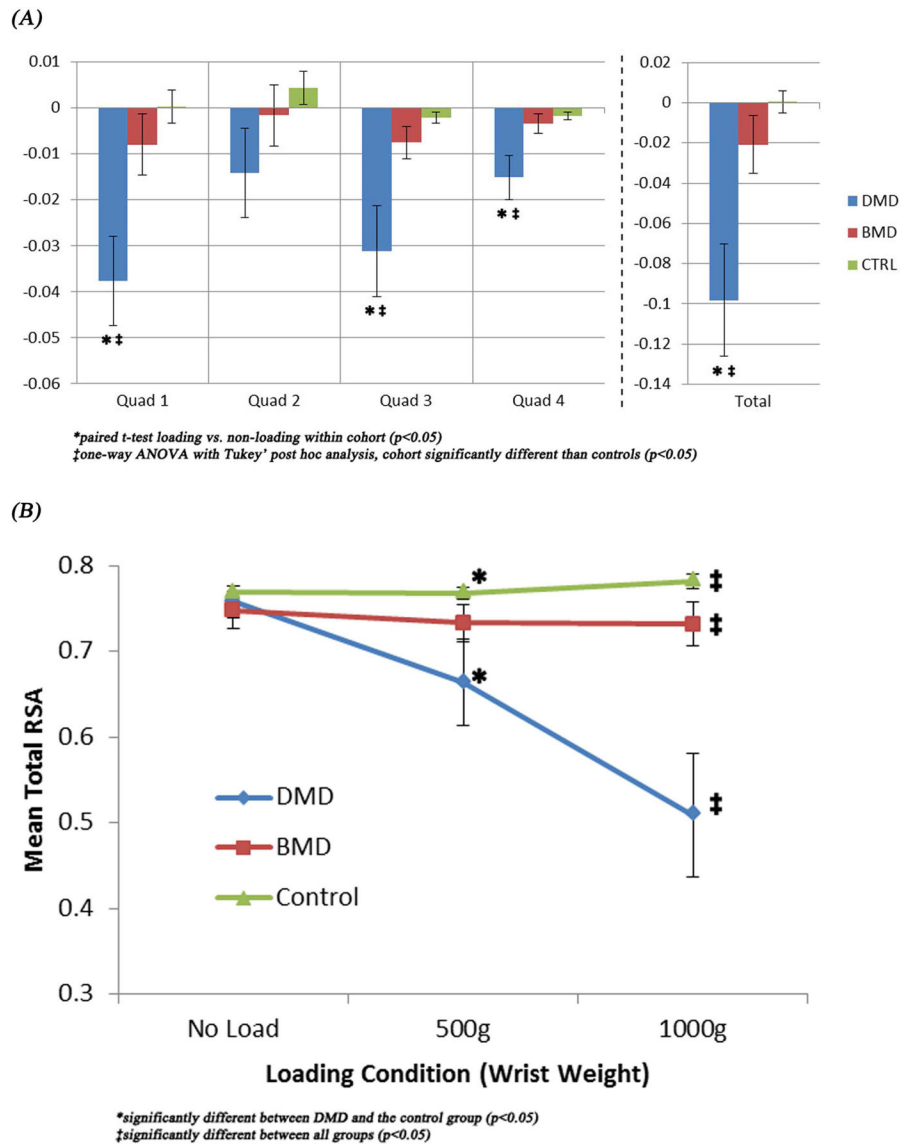
(A)

paired t-test loading vs. non-loading within cohort (p<0.05)
‡*one-way ANOVA with Tukey' post hoc analysis, cohort significantly different than controls (p<0.05)*

(B)

significantly different between DMD and the control group (p<0.05)
‡*significantly different between all groups (p<0.05)*

Fig. 6. Bar graph showing the reduction in mean total RSA (mean total RSA = mean total RSA with 500 g loading - mean total RSA with no loading) for DMD, BMD (Brooke grades 1 and 2) and control groups

(A) Respective mean total RSAs are shown with standard error bars. (B) Graph showing reduction in mean total RSAs with both 500- and 1000-gram wrist weights for those with Brooke grade 1: BMD (n=10), DMD (n=12), and healthy control cohorts (n=92).
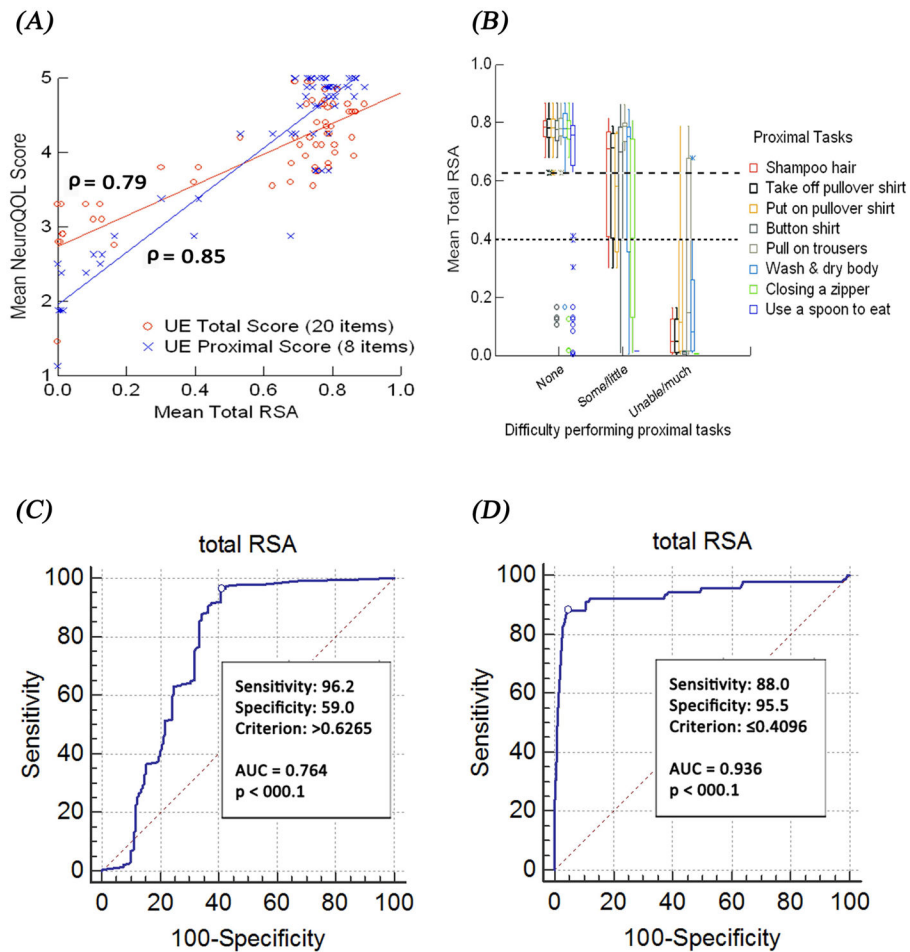
(A)

(B)

(C)

(D)

Fig. 7. Relationship between self-reported function on the NeuroQOL upper extremity function questionnaire and reachable workspace (RSA) in DMD

(A) A correlation of mean total RSA and mean scores from the total 20-item questions of the NeuroQOL or with the 8-questions that deal primarily with proximal upper extremity function. (B) Box-and-whiskers plot show the relationship between mean total RSA and self-reported degree of difficulty (none, some/little, or unable/much) experienced by individuals with DMD in performing various activities. (C) An ROC curve to determine the optimal RSA cut-off value for identification of individuals who have no difficulty performing proximal upper extremity associated ADL tasks is shown and is represented by the dashed line in (B). (D) An ROC curve to determine the optimal RSA cut-off value for identification of individuals who are unable to perform the listed proximal upper extremity-associated ADL tasks is shown and is represented by the dotted line in (B).

Table 1

Pearson correlation coefficients

Associations between age, height, and total RSA of left and right arms in the control, BMD, and DMD cohorts are shown.

	Controls (n=92)		BMD (n=26)		DMD (n=60)	
	Age	Height	Age	Height	Age	Height
RSA-Total	−0.077	−0.002	−0.394*	−0.122	−0.714*	−0.819*
P-value	ns	ns	0.046	ns	<0.0001	<0.0001

*
indicates significant difference with *P*<0.05

Table 2

Mean relative surface area (RSA) of the reachable workspace surface envelope

RSAs of the DMD, BMD, combined BMD/DMD, and control cohorts by quadrant and total area.

	Quad 1		Quad 2	Quad 3	Quad 4	TOTAL
	Contralateral Quadrant			**Ipsilateral Quadrant**		
Cohort (n)	**Upper**	**Lower**	**Lower**	**Upper**	**Lower**	
DMD (60)	$0.145^* \pm 0.095$	$0.107^* \pm 0.069$		$0.170^* \pm 0.104$	$0.181^* \pm 0.083$	$0.603^* \pm 0.326$
BMD (26)	$0.135^* \pm 0.074$	0.102 ± 0.049		0.194 ± 0.063	0.211 ± 0.045	$0.642^* \pm 0.203$
BMD/DMD (86)	$0.141^* \pm 0.089$	$0.105^* \pm 0.064$		$0.177^* \pm 0.094$	$0.190^* \pm 0.074$	$0.614^* \pm 0.294$
Control (92)	0.191 ± 0.037	0.129 ± 0.038		0.225 ± 0.015	0.226 ± 0.012	0.771 ± 0.058

Means ± SD and sample size (n) are presented for dominant and non-dominant sides (there were no significant side-to-side differences). DMD, BMD, BMD/DMD vs. Control by analysis of variance (ANOVA) with Tukey *post-hoc* analysis,

*
indicates significant difference with *P*<0.05

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Table 3

Mean relative surface area (RSA) by Brooke grade

Quadrant and total reachable workspace RSAs of the dystrophinopathy cohort by Brooke scale.

| | | Quad 1 | Quad 2 | Quad 3 | Quad 4 | TOTAL |
| | | Contralateral Quadrant | | Ipsilateral Quadrant | | |
Brooke Scale (n)	Mean Age	Upper	Lower	Upper	Lower	
1 (50)	16.24	0.190 ± 0.044	0.128 ± 0.042	0.230 ± 0.016	0.226 ± 0.014	0.774 ± 0.068
2 (18)	26.63	0.142 ± 0.085	0.127 ± 0.071	0.189 ± 0.073	0.221 ± 0.020	0.679 ± 0.207
3 (6)	40.44	0.017 ± 0.027	0.036 ± 0.036	0.055 ± 0.086	0.130 ± 0.069	0.239 ± 0.209
4 (4)	12.49	0.000 ± 0.000	0.032 ± 0.023	0.000 ± 0.000	0.058 ± 0.039	0.090 ± 0.061
5 (8)	16.05	0.000 ± 0.000	0.004 ± 0.011	0.000 ± 0.000	0.013 ± 0.017	0.017 ± 0.027

Means ± SD and sample size (n) are listed for dominant and non-dominant sides (there were no significant side-to-side differences).