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Longitudinal Study of Upper Extremity Reachable Workspace in Fascioscapulohumeral Muscular Dystrophy

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Abstract

Facioscapulohumeral Dystrophy (FSHD) results in slowly progressive strength impairment, especially the upper extremities. Recent discoveries regarding pathophysiology have led to exciting novel therapeutic strategies. To further facilitate drug development, improved FSHD outcome measures that are functionally-relevant and sensitive to longitudinal change will be critical. Recently, a motion sensor (Kinect)-based upper extremity outcome called 'reachable workspace' that provides a quantitative reconstruction of an individual's reachability was developed. In this study, changes in reachable workspace were tracked upwards for 5-years in 18 FSHD subjects. Results show −1.63%/year decline in total reachable workspace (p=0.144); with most notable decline in the above-the-shoulder level quadrants (upper-lateral Q3: −9.5%/year, p<0.001 and upper-medial Q1: −6.8%/year, p=0.063) with no significant changes in the lower quadrants (Q2,Q4). Reachable workspace declined more significantly if the subjects were challenged with 500g wrist weights: total reachable workspace: −1.82%/year, p=0.039; Q1: −7.20%/year, p=0.041; Q3: −8.09%/year, p=0.001. Importantly, reachable workspace outcome was also able to distinguish subgroups in FSHD: *mildly-* and *severely-affected* with essentially unchanging reachability over years, and *moderately-affected* who demonstrate the most detectable changes longitudinally. The study demonstrates utility for measuring declines in upper quadrant

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reachability, and provides enrichment/stratification of FSHD populations most likely to show treatment effects in clinical trials.

Keywords

Upper extremity function; Facioscapulohumeral Muscular Dystrophy; Kinect; Reachable workspace; Longitudinal

1. INTRODUCTION

Facioscapulohumeral muscular dystrophy (FSHD) is one of the most common inherited myopathic disorders, with an estimated prevalence of 1:15,000–1:20,000 (1–3). Recent studies have advanced our knowledge about the pathophysiology behind FSHD (4,5) and as a result, exciting therapeutic strategies to effectively treat FSHD are now being developed (6). However, in light of the substantial effort to develop meaningful treatments, FSHD clinical trials encounter major challenges including: (1) the establishment and maintenance of patient registries based on globally accepted datasets; (2) development and validation of patient-relevant outcome measures; and (3) further development and validation of molecular and imaging biomarkers.(7) Improvements in these areas are critical for the design of trials that will efficiently determine if new treatments are efficacious.

FSHD is a progressive disorder and most notably affects muscles of the face and upper extremity, with hallmark patterns of weakness in the shoulder girdle (8). Due to the wide-spectrum of disease phenotype present in FSHD (some individuals are severely affected while others can be very mildly affected), along with its relatively slow rate of progression (years to decades), development of effective and useful outcome measures have been challenging. This is especially true for upper extremity (UE) outcome measures. A relevant outcome measure in this population needs to be able to effectively characterize UE motor impairment *and* track slow rates of modest functional decline over time. In an attempt to address this, our group developed an UE outcome measure called the 'Reachable Workspace'. The reachable workspace utilizes 3-dimentional (3D) motion sensor technology (via the Kinect), and a series of arm motions to reconstruct an individual's 'reachable workspace' (essentially a frontal hemisphere of space around the shoulder that characterizes the extent of a person's reachability) (9). Thus far, the reachable workspace has shown excellent reliability (10), has been validated against the FSHD evaluation scale for upper extremity function (subscale II and III scores) (9), and has also been shown to be correlated to upper extremity strength (maximal voluntary isometric contraction, MVIC) in the FSHD population (11).

Here, we further extend our sensor-based reachable workspace outcome measure in FSHD and investigate whether the Kinect-based reachable workspace is also sensitive enough to accurately track disease progression longitudinally in this population. To accomplish this, UE function was tracked for periods of up to 5 years in a cohort of FSHD patients. At various time points during the 5 years, each individual's reachable workspace, FSHD evaluation scores, and Brooke scale scores were assessed. Another objective was to identify

populations most likely show declines in reachable workspace for the purposes of future stratification and subject enrichment for clinical trials.

2. MATERIAL AND METHODS

2.1 Study Participants

A total of 18 subjects with FSHD (7 women, 11 men) participated in this prospective, longitudinal study (duration ranged from 8 months to 5 years; mean of 2.5yrs and standard deviation of 471 days). For patient convenience, data collections coincided with each patient's scheduled clinical visits, with efforts made to collect data at regular intervals. However, due to patient's rescheduled or missing appointments, data collection intervals were varied. All FSHD participants were recruited from a regional neuromuscular disease clinic (UC Davis Clinic), who carried the diagnosis of FSHD and underwent diagnostic workup as well as genetic confirmation (contraction of D4Z4 repeats). In addition to clinical outcomes (see below), demographic and anthropometric information (age, gender, ethnicity, hand-dominance, height, and weight) was also collected from each subject. The study protocol was approved by the University IRB for human protection and privacy for research. Consent was obtained from all subjects or guardians prior to study participation.

2.2 Clinical Outcome Measures Collected

The FSHD evaluation scale (12) and the Brooke upper extremity function scale (13) were collected at each visit in conjunction with each subject's reachable workspace. Both the FSHD evaluation and the Brooke scales were performed according to standard published protocols. Briefly, total FSHD evaluation scores range from 0 to 15, representing scores from 6 sections measuring the strength and functionality of: (I) facial muscles (score: $0 - 2$); (II) scapular girdle muscles ($0 - 3$); (III) upper limb muscles ($0 - 2$); (IV) leg muscles ($0 - 2$); (V) pelvic girdle muscles ($0 - 5$); and (VI) abdominal muscles ($0 - 1$) (12). For this study, we calculated both the total FSHD evaluation score, and a summated sub-score from sections II and III (scapular and upper limb sub-scores) as a relevant, focused measure of upper limb function. The Brooke UE scale scores range from 0 to 6 points, based on the extent that one can mobilize their arms (13). Reachable workspace for each arm was also collected at each study visit. Participants performed the reachable workspace protocol for each arm, first without wrist weights (non-weighted) and then with 500g wrist weights (weighted). All study participants were provided ample rest in between assessments.

2.3 Reachable Workspace Analysis

The 3D reachable workspace for each arm (dominant and non-dominant) was reconstructed from the motion data acquired from the Kinect sensor, following our previously published protocol (Figure 1) (9–11). After completion of the protocol, each participant's reachable workspace is automatically displayed via four quadrants (Q1–4) per arm. The four quadrants are enumerated and colored for ease of interpretation as shown in Figure 1C: orange/Q1 represents the upper medial, green/Q2 represents the lower medial, blue/Q3 represents the upper lateral, and pink/Q4 represents the lower lateral quadrants respectively. We calculated total reachable workspace surface area (m^2), as well as areas for each of the quadrants. To allow for comparison between individuals, we normalized data to each subject's Kinect-

extracted arm length to obtain relative surface area, RSA (see previously published studies for more detailed and already validated methodology) (9–11). Comparisons between the arms (dominant vs. non-dominant) showed no statistical difference (data not shown; similar to previous data (9). Thus, averaged reachable workspace data (between arms) for each individual was used for analyses. The present study followed the same methodology that has been validated in our previously published studies for FSHD (10,11).

2.4 Statistical Analysis

To evaluate longitudinal change over time in our cohort, mixed-effect (ME) analysis was utilized. This model takes into account both fixed and random effects, and is particularly suitable for interpretation of longitudinal clinical data where incomplete data from missed appointments are often encountered. For this study, a standard mixed-effects model for panel data was used (xtmixed *var* time || id:) assuming an independent covariance structure for all clinical measures (FSHD scale, Brooke scale) and reachable workspace data (Q1–4 RSA, and total RSA). Stata 14.0 statistical software was used for all analysis, and P-values of < 0.05 was accepted as the level of significance (denoted by *) for all statistical analyses.

3. RESULTS

3.1 Study cohort characteristics

Our study cohort represented males and females between the ages of 14–75 (average age of 47), with males comprising a slight majority (61.1%; Table 1). At the time of study entry 94.4% were ambulatory; with an average FSHD evaluation total and subscale scores (sections II & III only) of 8 and 5 respectively; and an average Brooke score of 3 (range 1–5).

3.2 Longitudinal FSHD Evaluation Using Standard Measures of Upper Limb Impairment

Longitudinal FSHD evaluation scale upper extremity sub-scores (Supplemental Figure 1A) and Brooke scores (Supplemental Figure 1B) demonstrate little to no discernable change over the course of the study. Indeed, only 3 out of the 18 participants via the FSHD evaluation scale, and 8 out of 18 via the Brooke scale showed any change in score at all during the 5 year study period. Two high functioning participants were noted in the study's cohort, and were labeled with solid (ID: 201002) and dotted (ID: 201017) arrows throughout the figures. No statistically significant change was found over the study's follow up period in Brooke or FSHD evaluation scales when analyzed either with (Supplemental Table 1A: p=0.810 for FSHD; p=0.988 for Brooke) or without the two high functioning individuals (Supplemental Table 1B: p=0.668 for FSHD; p=0.888 for Brooke).

3.3 Longitudinal Change in Reachable Workspace (non-weighted assessments)

Figure 2 shows the change in reachable workspace for each participant (separated by quadrants) over the study period. In the un-weighted condition, a decline in reachability for the upper medial Q1 (Figure 2A, Table 2A; p=0.063) and statistically significant decline in the upper lateral Q3 quadrants (Figure 2C, Table 2A; p= 0.000) were noted. No change in reachable workspace was evident in the lower 2 quadrants (Figure 2B & 2D, Table 2A for Q2, p=0.319 and Q4, p=0.334). The average slope of reachable workspace (RSA) decline for

each quadrant can be seen by the dotted black thick lines throughout Figure 2. Using data from Table 2, we can calculate the average rate of change per year (% RSA change/year) for each quadrant. There is a 6.6% RSA decline in Q1, 1.9% increase in Q2, 9.3% decline in Q3, and a 0.74% decline in Q4. The two high functioning participants noted above with total RSA values greater than 0.80 (subjects 201002 & 201017) also displayed high functionality via the reachable workspace over the study follow up period. If these two high functioning subjects were removed from analyses, both Q3 *and* Q1 displayed significant RSA declines over time (Table 2B; p=0.000 and p=0.016 respectively).

3.4 Longitudinal Change in Reachable Workspace When Challenged (with 500g wrist weights)

When 500g wrist weights were added during reachable workspace evaluation, there was a more noticeable decline in reachable workspace over time. When looking at the entire cohort, in addition to Q3 RSA continuing to show a significant decline (Figure 3C; Table 2A, decline of 8.09% per year, p =0.001), there was also a significant decline in Q1 (Figure 3A; Table 2A, 7.20% RSA decline per year, p=0.041). No significant changes were seen in Q2 or Q4 during the 500g weighted assessments (Figure 3B & D, Table 2A: increase of 1.40% RSA and decline of 0.76% RSA per year, p=0.443 and p=0.241 respectively). However, Q2 started to display performance differences (Figure 3B) between individuals with these weighted assessments (a trend not seen in the non-weighted assessments). Again, if we removed the two high functioning individuals from analysis, decline rates were enhanced in Q1, Q3 and total RSA (Table 2B: 15.78% decline per year, p=0.047 for Q1; 12.75% decline per year, p=0.002 for Q3; and 3.04% decline per year, p=0.016 for total RSA).

3.5 Longitudinal Change in Total Reachable Workspace

If we look at the total RSA (all 4 quadrants together) there was a 1.63% RSA decline in total reachable workspace (p=0.144) across all subjects in the unweighted condition (Figure 4A; Table 2A, p=0.144), and a significant 1.82% RSA decline in the total reachable workspace in the weighted condition (Figure 4B; Table 2A, p=0.039). Given our results, the totality of reachable workspace at baseline was also assessed as a potential stratification or enrichment criteria to identify those FSHD subjects most likely to show significant declines in upper quadrant and total RSA over time. The study results demonstrated consistent, steady changes over time in individuals that had total RSA values at baseline of lower than 0.70, but higher than 0.20 (designated as *moderately-affected* FSHD individuals by total RSA). If we analyzed this group of FSHD individuals (0.2 < total RSA < 0.7) alone, we see significant declines in Q1 (12.66% RSA decline, p=0.015), Q3 (12.97% RSA decline, p=0.000) and total RSA (2.74% RSA decline, p=0.047), while no significant changes were detected in Q2 (1.73% RSA increase, p=0.349) or Q4 (1.39% RSA decline, p=0.084) (Supplemental Table 2A). In contrast, the higher individuals with baseline RSA values greater than 0.70 and those with floor values of 0.20 and lower did not show changes in either upper quadrant RSA or total RSA. During weighted assessments similar trends were seen. Significant declines in Q1 (15.44% RSA decline, p=0.044), Q3 (8.37% RSA decline, p=0.002) and total RSA (3.02% RSA decline, p=0.011) were present, with no significant changes in Q2 (0.05% RSA increase, p=0.980) or Q4 (1.12% RSA decline, p=0.121)(Supplemental Table 2B).

Figure 5 and 6 show graphical output examples of Q1–4 for each arm in a moderately affected FSHD individual over the 4 years of follow up for this subject. The decline in Q1 and Q3 for both arms without any weights is evident (Figure 5A and Figure 6A for the left and right upper extremity respectively). The decline in these quadrants is further enhanced when 500g wrist weights were added (Figure 5B for left, Figure 6B for right).

4. DISCUSSION

The clinical course of FSHD is characterized by a relatively stereotypical presentation and gradual development of muscle weakness across multiple body regions, with significant predilection for the shoulder girdle (8,14). This study's data show that the reachable workspace outcome measure is able to detect slowly changing upper extremity function in FSHD patients while the existing ordinal measures (FSHD evaluation scale and Brooke scale) that the study evaluated were unable to detect consistent changes. It also appears that the upper quadrants of reachable workspace will be the best candidates for use as a primary endpoint or prioritized secondary endpoints in FSHD clinical trials.

Additionally, through this longitudinal study using the novel reachable workspace outcome, new information on the pattern and extent of reachability decline in FSHD was observed. The study's findings reinforce what has long been observed clinically regarding the significant loss of overhead reachability in FSHD patients; however, the study adds new detailed information regarding the extent and pattern of loss as well as the rate of above-shoulder-level reachability decline that were previously unknown.

The study results mirror what would be expected and show a modest 1.6% decline per year in total reachability (total RSA); with the most notable rate of decline in the upper quadrants Q3 (upper lateral: 9.5% per year) and Q1 (upper medial: 6.8% per year) compared to the lower quadrants (Q2 and Q4). These reductions in reachability are consistent with our previous cross sectional work in FSHD population (9) that showed disproportionate reductions in Q1 and Q3 reachable workspace, but not Q2 and Q4, as UE function worsened. Although it is a different neuromuscular condition than FSHD, a follow up study in amyotrophic lateral sclerosis (ALS) also demonstrated similar pattern of reductions in Q3 reachability in a one-year longitudinal study. The reductions in upper quadrant reachability were substantial in ALS as would be expected for a rapidly progressive neuromuscular condition (15).

Although the reachable workspace assessment is limited to the proximal UE range of motion, this study's finding of a total upper extremity reachability decline of approximately 2% are also comparable to other FSHD longitudinal studies showing progression of disease (8,16,17). The most recent study by Stubgen and Stipp (17) shows a 4% decrease in overall muscle strength at the 5 year mark. This was calculated by averaging composite MMT scores from 18 different muscles in the upper and lower extremities. This study also found a 3.1% decline in activities of daily living after 5 years. Kilmer et al. (8) and the FSH-DY group (16) also found slow, but steady, declines in muscle strength via composite muscle testing.

Another finding of this longitudinal FSHD natural history study is that detection of gradual decline in reachability can be even further enhanced by using a simple loading condition (500 gram wrist weight). The yearly decline in reachable workspace for the entire FSHD cohort was a modest 1.6% for total RSA and 6.6% for Q1, although neither were statistically significant. The only significant decline was seen in Q3 at 9.3% per year. However, under a 500 gram wrist weight loading condition, yearly declines in reachable workspace were enhanced for the entire FSHD cohort. Under this 500g weighted condition, total RSA, Q1 and Q3 all showed statistically significant declines at 1.82%, 7.02% and 8.09% respectively. These findings indicate that by challenging the system (UE strength) to tease out subtle weaknesses, we are able to expose smaller-scaled, but nevertheless present, weaknesses in UE function and monitor the different rates of decline over time.

Our results also allude to the possibility that our sensor-based reachable workspace outcome may be sensitive enough to detect distinct subpopulations of FSHD patients more likely to show changes in total RSA, Q1 and Q3 over a shorter time period. The moderately impaired population of FSHD patients with baseline total RSA between 0.20 and 0.70 were more likely to show predictable declines over time. This baseline characteristic could be used to categorize or enrich clinical trial populations for a tendency to predictably change over time, and could also be used as a stratification factor for analyses. The mildly affected individuals in our cohort were essentially normal in terms of the reachable workspace (in total RSA and Qs1–4) and displayed minimal change throughout the study follow-up duration. It appears that those with higher baseline RSA values closer to normal (RSA > 0.70), *and* those with near floor values of reachable workspace (total RSA below 0.20), are less likely to change over time.

Pharmacologic interventions that stabilize muscle function are best tested in populations with predictable declines. This is based on the presumption that many treatments are aimed at slowing or halting disease progression; and only those displaying active, measurable rates of progression can offer accurate and reliable data regarding treatment or drug effectiveness (17). Treatments that *improve function* and reachable workspace will also show more robust effects in a population that is predictably declining over time. Patients with near normal ceiling values of reachable workspace may not demonstrate treatment benefits using this measure even if muscle function were positively impacted with treatment, and on the other end of the severity spectrum, those with lower floor values of reachable workspace may have limited residual muscle substrate targets available for the therapeutic agent, and thus making it challenging to demonstrate positive treatment effects.

The ability of the sensor-based reachable workspace to quantitatively track subtle, slowly progressing change in UE function, along with its ability to identify distinct sub-populations of FSHD patients more likely to decline over time, make it a valuable tool in the FSHD clinical trials toolbox. Indeed, it is low-cost and scalable making it particularly useful. For design of clinical trials, we believe that the reachable workspace outcome measure may be helpful to guide inclusion and exclusion criteria, for enriching study population of interest, as well as stratify subgroups of FSHD for analyses. The continuous variable of RSA additionally allows more sophisticated statistical analyses to take place. Due to the inherent objective and quantitative nature of the sensor-based reachable workspace, it will also be

extremely powerful for UE interventional/drug studies where high levels of accuracy and specificity are required. In all of these ways, the reachable workspace outcome has the ability to become an extremely useful tool for the FSHD field. Indeed, it would be complementary to newly developed imaging biomarker outcomes(18), functional composite scales (19), and other novel biomarker outcomes (20) currently under development.

As an exercise to aid in the utility of the reachable workspace outcome, we undertook an example power analysis assuming a two-armed, placebo controlled trial planned for repeated measure assessment, which is typical for a clinical trial. Sample sizes for two situations are presented: the first for situations using the entire FSHD spectrum (all FSHD patients at all phenotype ranges of UE function), and the second example for a study focused exclusively on those moderately affected, using reachable workspace entry criteria. For both scenarios, we based our calculations on a two-sided F test at 5% significance with a power of 80%. In these calculations, detectable changes are based on those quadrant(s) where significance was found (i.e. Q3 for the entire FSHD spectrum, and Q1, Q3 and total for the moderately affected group). It is also important to take into account that these numbers are an extrapolation of a possible clinical scenario, with specific assumptions. It is not meant to be considered a standard, as many trials will have variations in study design and other variables that need to be taken into consideration. We made two important assumptions while deriving these power calculations: (1) that the decline in UE for FSHD is fairly constant over years (and not fluctuating), and (2) entry at baseline will be a standardized point of disease status. For the first scenario using the entire FSHD spectrum, a sample size of 26 patients per study arm (i.e. total of a 52) with 5 annual repeated measurements (i.e. 1 at baseline and 4 follow-ups) would be needed to detect a significant difference in disease progression in Q3. For the second scenario focused on just those that are moderately affected, three different sample sizes can be calculated depending on the quadrant of interest. A sample size of 16 subjects per study arm (total of 32) with 5 annual repeated measurements would be required to detect significant difference in disease progression in Q3, while a sample size of 22 subjects per study arm (total of 44) with 5 annual repeated measurements would be required to detect significant difference in disease progression in Q1. In the moderately affected group, the total RSA was just slightly under the significance level and so a sample size of 44 subjects per study arm (total of 88) with 5 annual repeated measurements would be required to detect significant difference in disease progression overall. If a significant difference in all quadrants (Q1, Q3 and total RSA) is desired in this moderately affected group, one would need a sample size of 44 subjects per arm, with 5 annual repeated measurements to cover all potential differences. For all of these scenarios, the numbers per study arm would be higher if fewer repeated assessments were performed (i.e. 4 or 3 repeated measurements). Additionally, these numbers do not take into account drop-outs or withdraws due to failure to follow-up. The numbers presented here should be further adjusted to accommodate those situations. Although 12, 18 or 24 months is a standard duration for clinical trials, it may be challenging to see a distinct difference after treatment in FSHD even if the calculated numbers were used. This is a big challenge FSHD researchers have been facing with virtually all clinical outcome measures due to its slow progression and wide disease severity spectrum. A larger cohort study with follow-up duration that is similar to a typical clinical trial would provide more accurate data for sample size calculations.

4.1 Limitation and Future Studies

There are several limitations of this study, including small sample size. Only 18 individuals with FSHD from a regional neuromuscular clinic in the U.S. were involved in this study. In addition, there was limited number of patients with specific baseline total RSA values between 0.7 to 0.8 and above. This makes the definition of the upper boundary of the moderately severe group somewhat uncertain. However, the assembled study cohort is thought to be fairly representative of general FSHD demographics (in terms of males to female ratios, age ranges, and disease severity). Future longitudinal studies with larger sample sizes, that encompass broader ethnic, racial and geographic ranges, will be helpful to further validate our findings. Additionally, reachable workspace outcome measure is limited to assessment of upper extremity proximal range of motion, especially the shoulder and elbow, and therefore does not examine the distal hand/finger functions. However, for a disease such as FSHD with its predominant involvement of the shoulder girdle and proximal upper extremity, with relative sparing of the distal upper extremity function, the reachable workspace outcome measure may be an effective outcome measure regardless of this limitation. Incorporation of a distal hand functional measure would be complementary to the reachable workspace measure. Further studies investigating potential correlations to other upper extremity functional outcomes, activities of daily living functional status, or quality of life outcomes are also needed.

4.2 CONCLUSIONS

The reachable workspace outcome measure is a robust outcome measure that can effectively track slow rates of upper extremity functional decline over time in FSHD patients. It is objective and sensitive, making it superior to existing ordinal/categorical outcomes measures commonly used in clinical studies. Furthermore, its low cost and scalability makes it useful for large, multisite clinical trials. Although further studies investigating the full potential of the reachable workspace outcome measure and methodology are still underway, we believe it will be an excellent addition to the FSHD clinical trials toolbox, especially when coupled with other biological, radiologic, or functional composite outcomes measures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Highlights**

- The reachable workspace detects slowly progressive upper extremity change in FSHD

- Decline rates are more pronounced if subjects were challenged with wrist weights

- The reachable workspace is superior to existing scaled assessments over time

- The reachable workspace is useful for stratification for clinical trials
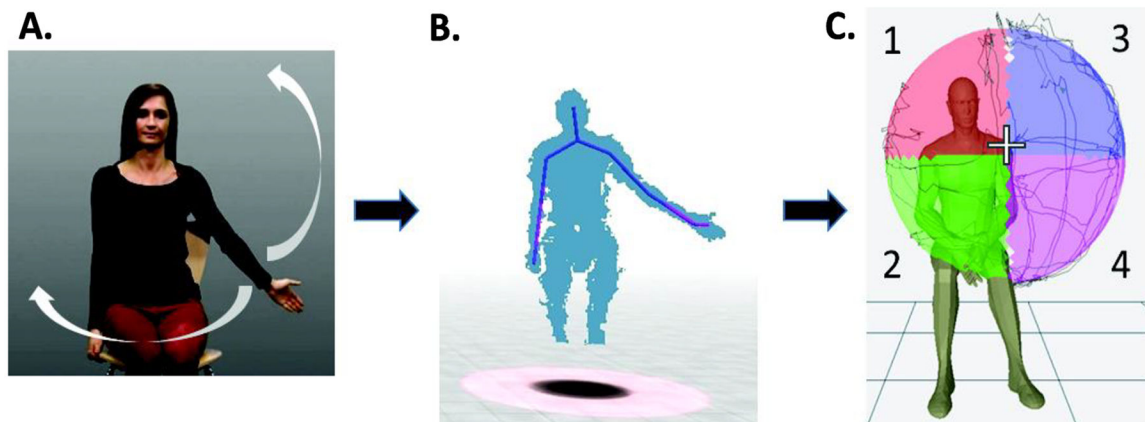
Figure 1. Example of Upper Extremity Motion Capture (reachable workspace) of the left arm, in this case.
(A) Example of participant's live body position and arm movements for reachable workspace recordings. (B) View of Kinect sensor's skeletal tracking of upper extremity movement. (C) 3D graphical output of arm motion and reconstruction of reachable workspace from Kinetic sensor recordings, separated into 4 different quadrants (1 through 4).
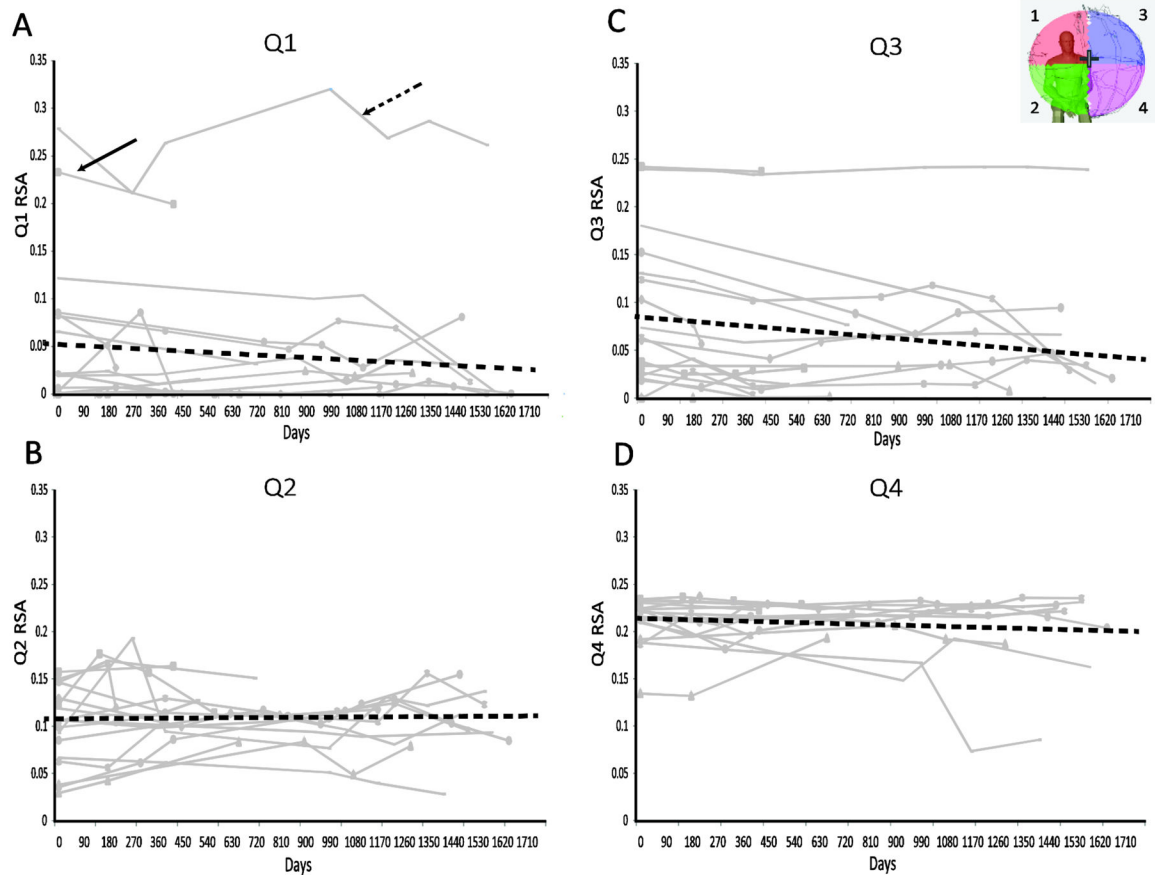
Figure 2. Reachable workspace over time without weights:
Average relative surface areas (RSAs) for all participants via each of the 4 quadrants. (A) Quadrant 1, upper medial area. (B) Quadrant 2, lower medial area. (C) Quadrant 3, upper lateral area. (D) Quadrant 4, lower lateral area. Solid arrow (201002) and dotted arrow (201017) are high functioning participants. Dotted black lines in A-D represent the average slope of decline over the 5 year period. Mannequin in the upper right hand corner displays the 4 representative quadrants.
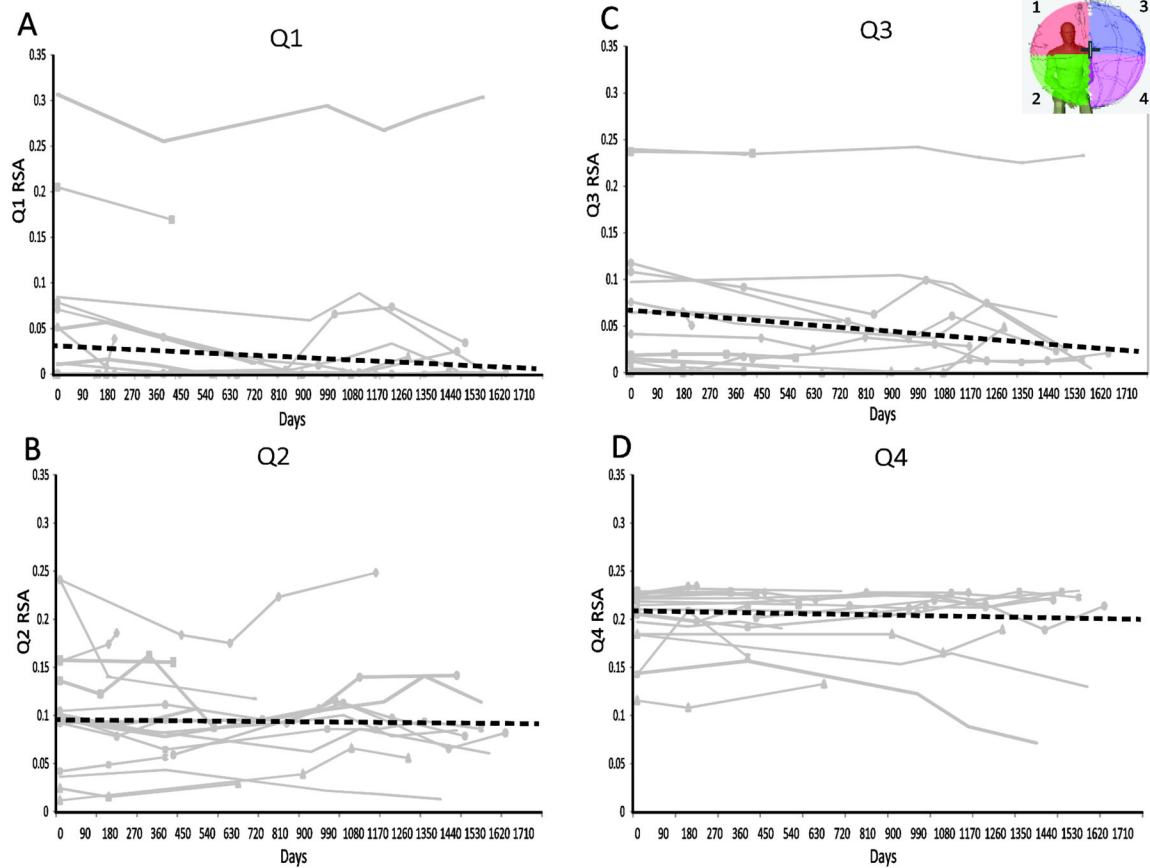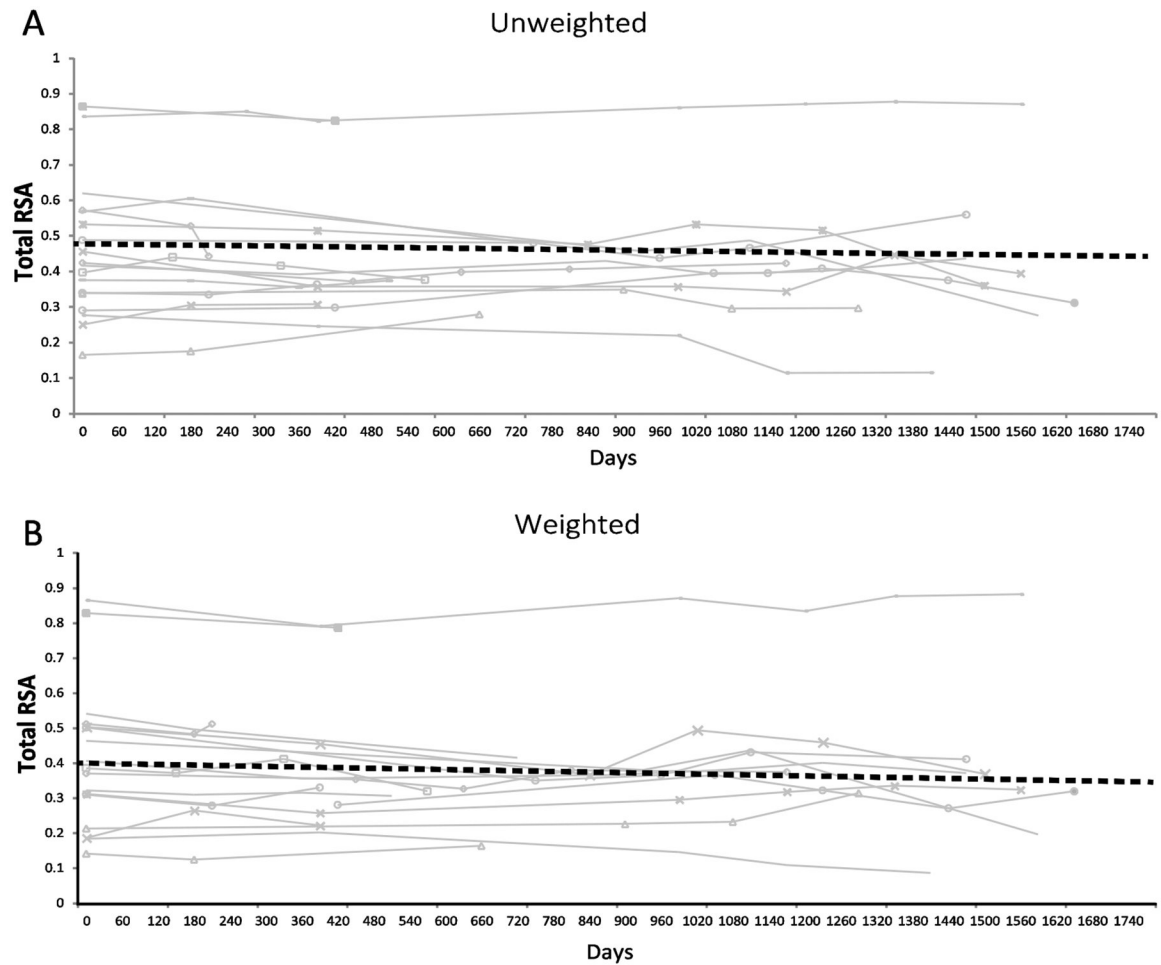
Figure 3. Reachable Workspace over time under loading condition:
Average relative surface areas (RSAs) for all participants via each of the 4 quadrants with 500g wrist weights. (A) Quadrant 1, (B) Quadrant 2, (C) Quadrant 3, and (D) Quadrant 4. Solid arrow (201002) and dotted arrow (201017) are high functioning participants. Dotted black lines in A-D represent the average slope of decline over the 5 year period. Mannequin in the upper right hand corner displays the 4 representative quadrants

Figure 4. Total reachable workspace over time:
Average total reachable workspace for entire cohort for (A) non-weighted assessments and (B) weighted assessments. Solid arrow (202002) and dotted arrow (202017) are represent high functioning participants. Dotted black lines in A and B represent the average slope of decline over the 5 year period.

A

subject 201005: left side, No weight

B

subject 201005: left side, 0.5kg weight
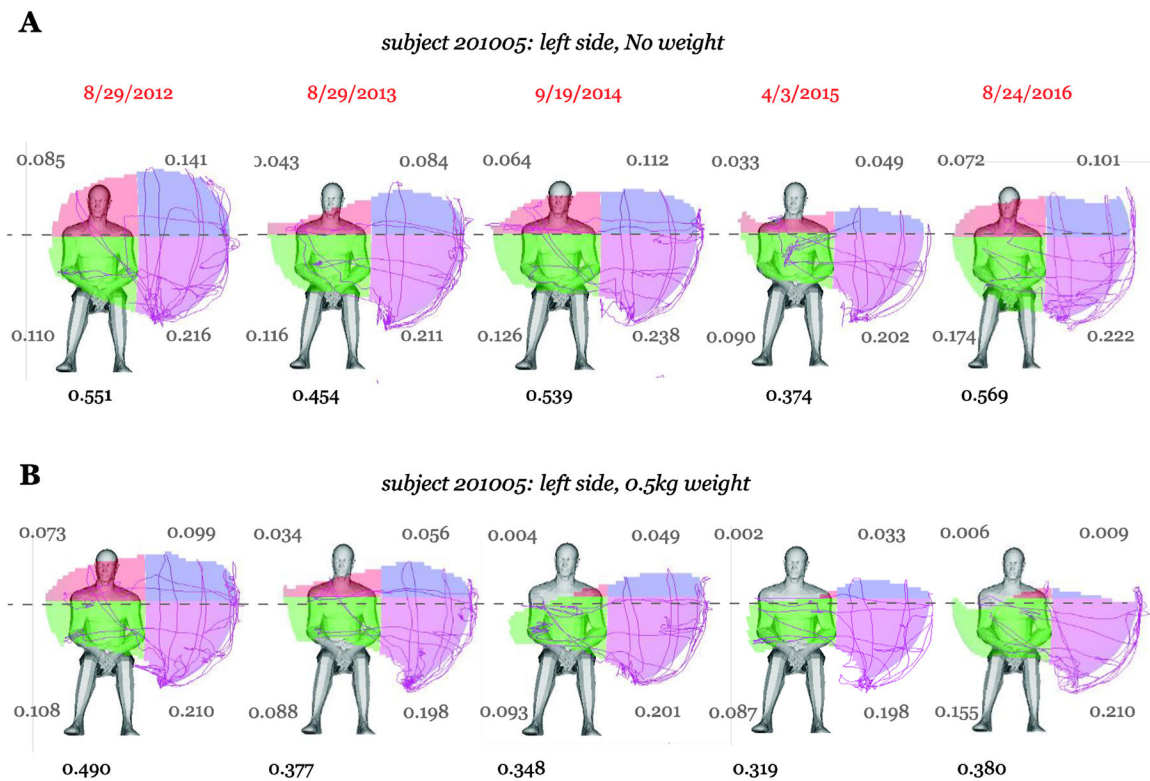
Figure 5. Graphic output of Q1-Q4 for *left* upper extremity in a moderately affected FSHD patient over 4-year follow up.

Reachable workspace outputs for (A) without weights and (B) with 500g weights. A decline in Q1 (orange) and Q3 (blue) is evident for weighted and unweighted assessments, with a larger decline when loading condition is applied.

A *subject 201005: right side, No weight*

8/29/2012   8/29/2013   9/19/2014   4/3/2015   8/24/2016

| 0.164 | 0.086 | 0.113 | 0.055 | 0.085 | 0.045 | 0.084 | 0.070 | 0.088 | 0.086 |

| 0.208 | 0.060 | 0.234 | 0.084 | 0.237 | 0.109 | 0.228 | 0.114 | 0.223 | 0.135 |

| 0.518 | 0.487 | 0.476 | 0.497 | 0.546 |

B *subject 201005: right side, 0.5kg weight*

| 0.136 | 0.069 | 0.113 | 0.064 | 0.060 | 0.026 | 0.040 | 0.018 | 0.038 | 0.044 |

| 0.227 | 0.077 | 0.234 | 0.093 | 0.227 | 0.098 | 0.224 | 0.127 | 0.229 | 0.128 |

| 0.509 | 0.503 | 0.411 | 0.409 | 0.439 |
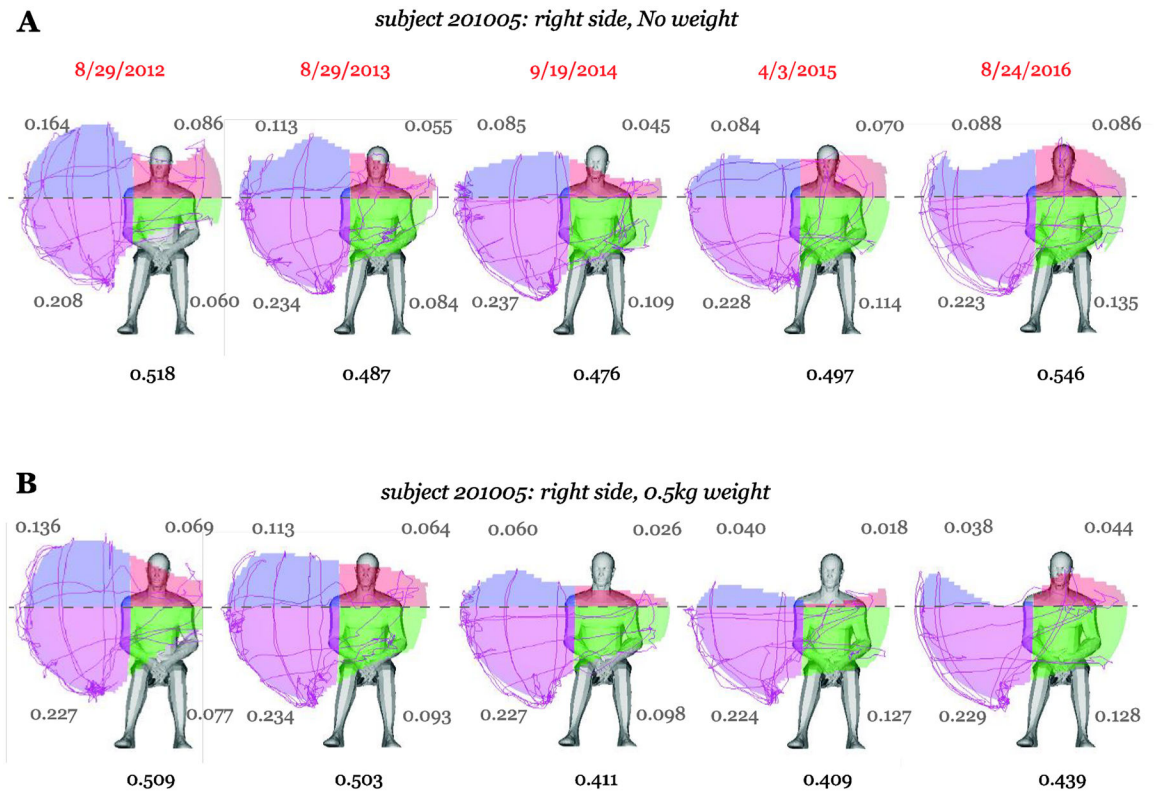
Figure 6. Graphic output of Q1-Q4 for *right* upper extremity in a moderately affected FSHD patient over the 4-year follow up.

Reachable workspace outputs for (A) without weights, and (B) with 500g weights. Decline in Q1 (orange) and Q3 (blue) is evident, compared to Q2 (green) and Q4 (pink). Declines in Q1 and Q3 are larger when assessments were weighted.

Table 1.

Cohort characteristics:

Demographic information and disease characteristics were collected at study entry from all participating individuals. Totals (represented by %), averages and ranges (where applicable) are provided.

	Total %	Average *(where applicable)*	Range *(where applicable)*
Demographic Characteristics			
Male	61.1 (*11*)	-	
Age (yrs)		47	
< 20	16.7 (*3*)	-	
21 – 60	44.5 (*8*)	-	
61 +	27.8 (*5*)	-	
unknown	11.1 (*2*)	-	
Race			
White/causasian	88.9 (*16*)	-	
Asian	5.6 (*1*)	-	
Black	5.6 (*1*)	-	
Ethnicity			
Hispanic	5.6 (*1*)		
Disease Characteristics			
FSHD eval (total score)	-	7.8	1 – 15
FSHD subscore (arm only)	-	3.5	0 – 5
Brooke's score	-	3	1 – 5
Ambulatory	94.4 (17)	-	
Handedness			
Right	88.3 (15)	88.3 (*15*)	
Left	16.7 (3)	16.7 (*3*)	
Body characteristics			
Height (cm)	-	172.4	
Weight (kg)	-	77.4	
BMI	-	26.1	

Table 2.

Mixed-Effects analysis of reachable workspace:

Longitudinal mixed-effects analysis was run on each quadrant (Q1–4) and the total RSA for unweighted (white rows) and weighted assessments (grey rows). Intercept (mean), slope, p-vaules, and calculated rates are displayed for analysis on the entire cohort (A) and after high functioning participants were removed (B). * represents p-value of <0.05. Slope units are in days.

A.

	Intercept ± S.E.	Slope ± S.E.	Calculated Rates (% per year)	Slope P-value
Quadrant 1	0.05511 ± 0.01764	$-0.00001 \pm 0.0541e^{-04}$	-6.62	0.063
Quadrant 1 weighted	0.04417 ± 0.01765	$-0.0871e^{-04} \pm 0.0426e^{-04}$	-7.20	$0.041*$
Quadrant 2	0.10415 ± 0.00815	$0.054500e^{-04} \pm 0.0546e^{-04}$	$+1.91$	0.319
Quadrant 2 weighted	0.09185 ± 0.00997	$0.035200e^{-04} \pm 0.0459e^{-04}$	$+1.40$	0.443
Quadrant 3	0.08285 ± 0.01661	$-0.000021 \pm 0.0566e^{-04}$	-9.25	$0.000*$
Quadrant 3 weighted	0.06316 ± 0.01650	$-0.000014 \pm 0.0413e^{-04}$	-8.09	$0.001*$
Quadrant 4	0.21091 ± 0.00665	$-0.0426e^{-04} \pm 0.0442e^{-04}$	-0.74	0.334
Quadrant 4 weighted	0.20123 ± 0.00848	$-0.0421e^{-04} \pm 0.0359e^{-04}$	-0.76	0.241
Total	0.44781 ± 0.04147	-0.00002 ± 0.00001	-1.63	0.144
Total weighted	0.40010 ± 0.04379	-0.00002 ± 0.000011	-1.82	$0.039*$

B.

	Intercept + S.E.	Slope + S.E.	Calculated Rates (% per year)	Slope P–value
Quadrant 1	0.03252 ± 0.00759	$-0.000012 \pm 0.0500e^{-04}$	-13.47	$0.016*$
Quadrant 1 weighted	0.01952 ± 0.00553	$-0.0844e^{-04} \pm 0.0424e^{-04}$	-15.78	$0.047*$
Quadrant 2	0.09956 ± 0.00838	$0.0678e^{-04} \pm 0.0527e^{-04}$	$+2.48$	0.198
Quadrant 2 weighted	0.08876 ± 0.01034	$0.0860e^{-04} \pm 0.0490e^{-04}$	$+3.54$	0.861
Quadrant 3	0.06344 ± 0.01030	$-0.0000231 \pm 0.0625e^{-04}$	-13.20	$0.000*$
Quadrant 3 weighted	0.04094 ± 0.00785	$-0.0000143 \pm 0.0454e^{-04}$	-12.75	$0.002*$
Quadrant 4	0.20982 ± 0.00731	$-0.0582e^{-04} \pm 0.0497e^{-04}$	-1.01	0.243
Quadrant 4 weighted	0.19855 ± 0.00920	$-0.0522e^{-04} \pm 0.0402e^{-04}$	-9.60	0.194
Total	0.40036 ± 0.02649	-0.000027 ± 0.000016	-2.47	0.093
Total weighted	0.34853 ± 0.02660	-0.000029 ± 0.000012	-3.04	$0.016*$