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3-Dimensional Kinematic Comparison of Arm Movements between an Individual with NGLY1 Deficiency and a Neurotypical Individual

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Abstract

NGLY1 Deficiency is an ultra-rare autosomal recessively inherited disorder. Characteristic symptoms include among others, developmental delays, movement disorders, liver function abnormalities, seizures, and problems with tear formation. Movements are hyperkinetic and may include dysmetric, choreo-athetoid, myoclonic and dystonic movement elements. To date, there have been no quantitative reports describing arm movements of individuals with NGLY1 Deficiency. This report provides quantitative information about a series of arm movements performed by an individual with NGLY1 Deficiency and an aged-matched neurotypical participant. Three categories of arm movements were tested: 1) open ended reaches without specific end point targets; 2) goal-directed reaches that included grasping an object; 3) picking up small objects from a table placed in front of the participants. Arm movement kinematics were obtained with a camera-based motion analysis system and "initiation" and "maintenance" phases were identified for each movement. The combination of the two phases was labeled as a "complete" movement. Three-dimensional analysis techniques were used to quantify the movements and included hand trajectory pathlength, joint motion area, as well as hand trajectory and joint jerk cost. These techniques were required to fully characterize the movements because the NGLY1 individual was unable to perform movements only in the primary plane of progression instead producing motion across all three planes of movement. The individual with NGLY1 Deficiency was unable to pick up objects from a table or effectively complete movements requiring crossing the midline. The successfully completed movements were analyzed using the above techniques and the results of the two participants were compared statistically. Almost all comparisons revealed significant differences between the two participants, with a notable exception of the 3D initiation area as a percentage of the complete movement. The statistical tests of these measures revealed no significant differences between the two participants, possibly suggesting a common underlying motor control strategy. The 3D techniques used in this report effectively characterized arm movements of an individual with NGLY1 deficiency and can be used to provide information to evaluate the effectiveness of genetic, pharmacological, or physical rehabilitation therapies.

Keywords

NGLY1 Deficiency, Developmental Disorders, Kinematics, 3 Dimensional Analyses

1. Introduction

NGLY1 Deficiency is an autosomal recessively inherited disorder, initially described in humans by Need, *et al.*, [1]. To date, just over 100 individuals have been confirmed to have NGLY1 deficiency, making it an ultra-rare disorder. In a recent review article, Pandey *et al.*, [2] tabulated the characteristics (age, sex, NGLY1 genotype and phenotypes) of 56 individuals with NGLY1 Deficiency. NGLY1 Deficiency presents with multiple characteristic symptoms that prominently include microcephaly, developmental delays, abnormalities on EEG, liver function abnormalities, chronic functional bowel issues, small hands and feet, strabismus as well as hypolacrimia or alacrimia [2] [3]. The quality of movements of individuals with NGLY1 Deficiency has been described as a hyperkinetic movement disorder and may include dystonic, myoclonic, dysmetric, and athetoid movement components [4]. Tremors during voluntary movements have also been reported. Adding complexity to the underlying movement disorder(s) may be seizures, joint hypermobility, and neuropathies, all of which are commonly reported with NGLY1 Deficiency [2] [4]. Furthermore, it has been reported that over half of a studied cohort (29 individuals, all over the age of six years) experienced fractures—most commonly in the lower extremities—which clearly impact movement ability and quality [5].

Findings from a registry study also provided additional information on NGLY1 Deficiency motor deficits, including the age of emergence as well as detailing the regression of multiple gross motoric developmental milestones in a cohort of NGLY1 Deficiency individuals [5]. These regressions were noted as gait abnormalities, and imbalance as well as fatigue from previous (peak) developmental milestones such as sitting, crawling, supported standing and walking [5]. To our knowledge, there have been no comprehensive, laboratory-based quantitative reports focused on the quality of movements of upper limb individuals with NGLY Deficiency. Arm movements are instrumental in many activities associated with quality of life, such as grooming and feeding. Quantitatively describing upper limb movements of individuals with NGLY1 Deficiency will aid in the understanding of the underlying motor control of these movements. Such understanding may lead to targeted pharmacological, genetic, or physical rehabilitation therapies as well as provide benchmark information to determine the efficacy of such therapies.

This investigation describes, in detail, the quantitative measures associated with a variety of upper limb movements from a single, non-ambulatory individual with NGLY1 Deficiency who displayed significant motoric disorders. Additionally, these measures are compared to an aged-matched neurotypical individual. Given the paucity of quantitative information about quality of movement in individuals with NGLY1 Deficiency, this investigation will add novel and important information to the literature. Our primary aim was to determine which movements the individual NGLY1 Deficiency participant could effectively complete as well as explore potential differences between the neurotypical and NGLY1 Deficiency participant. We were specifically interested in exploring whether 1) the movements of the two participants differed when the data of each participant was collapsed over all available movements; and 2) potential differences in movements of the (a) right arm; (b) left arm; (c) first attempt of each arm movement; (d) second attempt of each arm movement; (e) open-ended arm reaches; (f) goal-directed arm reaches. A secondary, but related aim, was to develop a comprehensive description—using 3-dimensional non-linear measures—of the completed movements. We firmly believe that answering the above questions using our comprehensive, quantitative measures provides critical insights into the quality of arm limb movements of an individual with NGLY1 Deficiency, as well as establishing a robust methodology that future investigators can utilize to assess movements.

2. Methods

2.1. Study Participants

The participant was a 19-year-old female diagnosed with NGLY1 Deficiency (see details below). The neurotypical control participant was an aged-matched, right-handed female with no incidence of neurological disorder as assessed by self-report. Hereafter, the participant with NGLY1 Deficiency will be labeled P1 and the neurotypical individual will be labeled P2. P2 Both participants provided written informed consent with consent for P1 being provided by her parents. The Institutional Review Boards of the University of Houston (00000855) and Baylor College of Medicine (H-35835) approved all procedures.

2.2. Clinical Characteristics of NGLY1 Deficient Participant

The NGLY1 participant in this study carries both a heterozygous frameshift variant c.1242 delT and a splice site affecting c.858 + 1G > A variant in the NGLY1 gene, detected by whole exome analysis. Her developmental trajectory was delayed from infancy and was first noted abnormal around 8 months. She achieved sitting only at 14 months, crawling at 19 months, and walking with a walker at 3 years of age. She had dystonia at both ankles necessitating the use of ankle foot orthoses from the age of 5 months onward. She developed more generalized hypertonia after 24 months, and at 36 months she developed scoliosis that progressed to such severity that it needed to be surgically addressed. At this point, she lost the ability to stand or walk independently. At the time of our assessment, she had a Gross Motor Function Classification System—Expanded & Revised (GMFCFS E&R) score of 4 and her highest level of gross motor skill was standing with support. Along with developing a generalized increase in muscle tone she started developing movement disorders that are typical for NGLY1 Deficiency which included tremor, choreo-athetoid movements, dysmetria during intentional reaches, and orofacial dyskinesias. The movement disorder became more pronounced over time. Although it was impossible to assess handedness using any typical techniques, PI’s parents indicated that it was their impression PI seemed to prefer to use her right hand.

2.3. Study Protocol

The data collection protocol consisted of a series of upper limb movements performed from a seated position. The movements were divided into three categories: 1) open-ended reaches, 2) object pick-up, and 3) goal-directed movements (**Table 1**). Open-ended movements were movements that did not require an action of the hand at the completion of the arm motion. Instead, the task itself was simply to move the arm in a specific motion (e.g., raising the arm above the head). Object pick-up movements required the participants to reach for *and* pick-up an object placed on an abdomen-level table. Goal-directed movements required that the participants reach and grasp an object that was presented (by hand) to them. All movements began with the participants’ hands resting in their laps, before performing the assigned action and then returning their hand(s) to their lap. Visual inspection of the movements revealed that P1 was not always able to begin with her hands entirely in her lap, but that her elbow was fully flexed prior to each movement. Each movement was performed twice, and prior to each movement, a research assistant demonstrated the action to be performed.

Prior to data collection, the participant was fitted with infrared reflective markers placed bilaterally on the upper limbs and trunk consistent with the Vicon® upper limb kinematic model. Movements of these markers were acquired with a Vicon® motion capture system. As the Vicon system included 16 cameras, no markers were obscured during any of the movements and the 100 Hz sample rate insured that even subtle movements were accurately collected. Surveillance video was also collected during each movement and shoulder, elbow, and wrist joint angles were computed using the Vicon® Nexus software.

2.4. Measures & Processing

During data collection it was readily apparent that P1's arms exhibited substantial movement in all three planes of motion (sagittal, frontal, and transverse). This necessitated computation of joint angles in three dimensions for both the shoulder and wrist. As we used the Vicon Nexus, software to compute joint angles, which only computes flexion and extension of the elbow, motion of the elbow was represented along a single axis.

Visual inspection of the hands time series data displayed tremor-like motions of varying frequencies and amplitude, in both the arm performing the action, as well as the uninvolved arm. As some human tremors have been reported to reach frequencies as high as 15 Hz [6], data were filtered with a custom MATLAB script® using a 2nd order Butterworth low-pass filter with a 20 Hz cutoff frequency. Further, evaluation of hand trajectory data revealed that movements were composed of two distinct phases. These phases were an 'initiation' phase—movements from the lap to end goal—and then a 'maintenance' phase consisting of movements starting at the end goal of movement until the time the hand began returning to the participant's lap (**Figure 1**). The initiation phase was composed of a combination of limb acceleration and decelerations that moves the hand toward the end-point of the movement prior reaching the maintenance phase. Onset of the initiation phase was determined with the use of a custom MATLAB script applied to the hand marker trajectories (placed on the first metacarpophalangeal joints, *i.e.*, index finger knuckle) of the arm that is performing the movement. The script "searches" through the data stream of the primary plane of motion for 25 consecutive samples of increasing marker trajectory displacement. When the criterion is reached, the initial sample of the 25 consecutive samples of increasing marker trajectory displacement is identified as the onset of movement. The offset of the initiation phase is identified as at least 5 consecutive samples of decreasing trajectory displacement. The completion of the movement is identified as 25 consecutive samples decreasing marker trajectory displacement with the initial sample of the 25 consecutive samples being identified as the moment of movement completion. The combination of the initiation and maintenance phases was labeled as a 'complete' movement. The primary plane was defined as the plane in which the hand moved through the greatest amount of displacement. For example, when reaching to grasp an object, the greatest motion is in the sagittal plane and was labeled as the primary plane. When the movement required the participants to either abduct or adduct their shoulders, the primary plane was identified as the frontal.

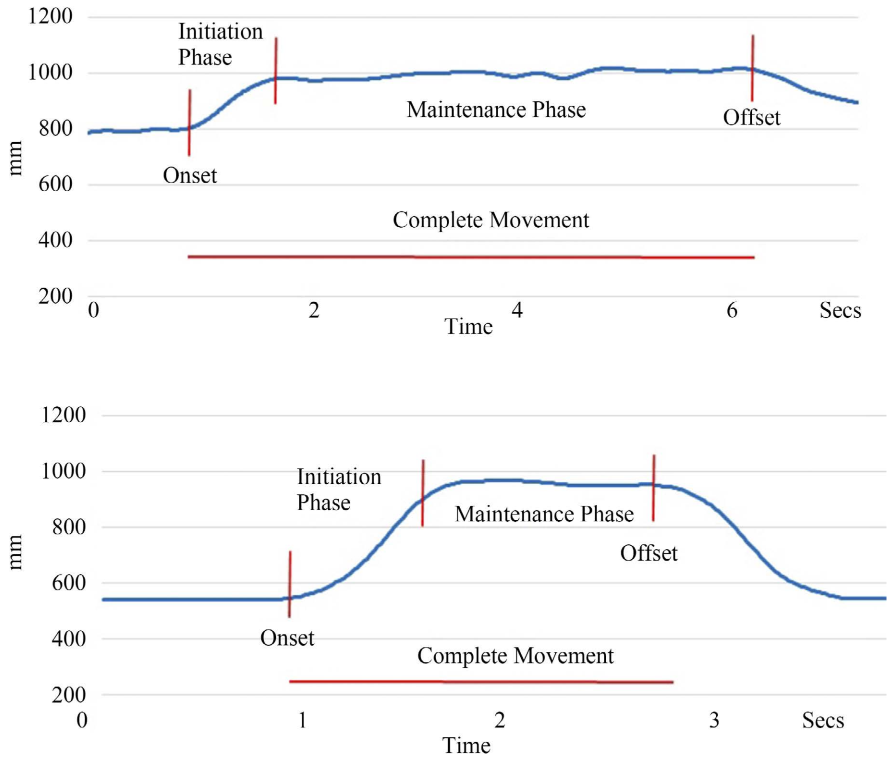


Figure 1. Exemplar hand movement profiles in the dominant plane of motion during an arm movement. Panel A is data from P1 and Panel B is data from P2. Note the differences in scale along the X-axis.

The duration and peak velocity of each initiation phase was calculated from hand trajectories in the primary plane of progression. Pathlength—here defined as total distance traveled across the X, Y and Z dimensions—was calculated for both the complete movements and initiation phases of the hand using a custom MATLAB® script. Given the prevalence of arm movements across all three planes, we used two 3D techniques to analyze the shoulder and wrist joint angle data; 3D area and 3D jerk cost—which allowed us to analyze limb kinematics fully—in three dimensions—and without compression or distortion errors that could result from only examining a single dimension. A custom MATLAB® script was also utilized to calculate the minimum 3D area completely encompassing movements of the shoulder and wrist joints for both the complete movements and the initiation phases [7] [8]. These areas were then used to determine the percentage area of total area that the initiation phase accounted for. This allowed us to normalize the movements across trials and participants, as data from each complete movement is transformed to represent 100% of the movement. This measure provides insights into the motor control of the movement. Finally, the 3D jerk costs of the hand trajectories, shoulder, and wrist angles, were calculated [9]. Jerk cost quantifies the ‘smoothness’ of a limb motion and represents the coordination of that movement [10].

To examine whether there were differences between the two participants, the data for each participant was collapsed over movement, arm, and reach attempt. Data were categorized into all right-handed movements, all left-handed movements, all first attempt movements, all second attempt movements, all open-ended movements, and finally, all goal-directed movements. Means, standard deviations (SD), and medians were tabulated for each participant of the above data arrangements.

2.5. Statistical Analysis

Data were checked for normality using the Kolmogorov-Smirnov test and equality of variance was checked using Levene's test. Although all data were normally distributed, not all data sets displayed homogeneity of variance. When data violated parametric assumptions, non-parametric Mann-Whitney U tests were used to test for differences in the measures between the two participants. When the homogeneity of variance was met, t-tests for independent samples were used to explore potential differences between the two participants. All tests were two-tailed and alpha was set at 0.05.

3. Results

As one of our aims was to provide a comprehensive report of quantitative information regarding the kinematics of the arm movements of an individual with NGLY1 Deficiency, there are a considerable number of data tables in the Results. Almost all of the statistical comparisons between participants 1 and 2 presented in the tables reflect significant differences between the participants, regardless of the measure. However, there are two notable exceptions to this. The first is observed in **Table 4**, panel B, which reports the 3D hand pathlength during the initiation phase of the movements where five of the seven comparisons do not reach significance. The second exception is observed in **Table 7** which presents the results of the comparisons of the initiation phase 3D area as a percentage of the 3D area of the Complete movement for both the shoulder and wrist. In this table, 13 of the 14 presented comparisons failed to reach statistical significance.

From a qualitative perspective, based on observation, the movements of PI displayed the stereotypical qualities of both athetoid and dystonic movements, as well as tremor. Interestingly, the hyperkinetic movements were most prevalent during the initiation of the arm movements, often combined with cervical dystonia causing a significant twisting of the neck. Generally, the disordered movements would be inhibited during the acceleration phase but would return during the maintenance phase of the movements. These disordered movements were observed on every movement regardless of the specific reaching task and the magnitude did not visibly change as a result of possible fatigue over the course of the testing. A recent report by Futrell and Layne [11], provides additional information specific to the characteristics of the observed tremor.

Table 1 lists the different movements the participants were asked to perform, which arm was used, how many attempts were made for each movement, and how many attempts were successful for P1. P2 was able to successfully complete all the tasks. **Tables 2-10** display summary statistics as well as the results of the statistical testing.

Table 1. Arm movements descriptions and the number of successful movements for P1.

Arm Movement*	Arm moved	#Completed Arm Movements	Picked-up/Grasped Object
Open-ended movements			
90˚ shoulder flexion with full elbow extension	Right	2	NA
90˚ shoulder flexion with full elbow extension	Left	2	NA
90˚ shoulder flexion with full elbow extension	Both	2	NA
180˚ shoulder flexion with full elbow extension	Right	2	NA
180˚ shoulder flexion with full elbow extension	Left	2	NA
180˚ shoulder flexion with full elbow extension	Both	2	NA
90˚ shoulder abduction with full elbow extension	Right	2	NA
90˚ shoulder abduction with full elbow extension	Left	2	NA
90˚ shoulder abduction with full elbow extension	Both	2	NA
Adduct arm across the midline to touch shoulder	Right	0	NA
Adduct arm across the midline to touch shoulder	Left	1	NA
Adduct arm across the midline to touch shoulder	Both	0	NA
Object pickup from table			
Pick up tennis ball	Right	2	1
Pick up tennis ball	Left	1	0
Pick up golf ball	Right	1	0
Pick up golf ball	Left	0	0
Pick up small toy car	Right	1	1
Pick up small toy car	Left	0	0
Pick up pen (horizontally placed on table)	Right	0	0
Pick up pen (horizontally placed on table)	Left	0	0
Pick up pen (vertically placed on table)	Right	0	0
Pick up pen (vertically placed on table)	Left	0	0
Goal-directed grasping			
Grasp tennis ball**	Right	2	0
Grasp tennis ball	Left	2	2
Grasp golf ball	Right	2	0
Grasp golf ball	Left	0	0
Grasp toy car	Right	2	0
Grasp toy car	Left	2	0
Grasp pen (Horizontally presented)	Right	2	1
Grasp pen (Horizontally presented)	Left	2	1
Grasp pen (Vertically presented)	Right	2	2
Grasp pen (Vertically presented)	Left	2	2
Grasp 14 cm diameter ring (Horizontally presented)	Right	2	2
Grasp 14 cm diameter ring (Horizontally presented)	Left	2	2
Reach through 14 cm diameter ring (Vertically presented)	Right	1	1
Reach through 14 cm diameter ring (Vertically presented)	Left	2	2

Figure 2 provides representative waveforms of the motion of the shoulder across the sagittal (x), frontal (y), and transverse planes (z). One of the objectives of this investigation is to present methodologies that can be used to characterize the multi-dimensional movements of individuals with NGLY1 Deficiency. To illustrate these methodologies, all of the figures were developed using either shoulder joint angles or hand trajectories captured during the same movement (hands in lap to 90° shoulder flexion with full elbow extension reach). This allows the reader to see how the same data is represented by the various analysis techniques used in this report. Additionally, although there is only a single exemplar figure representing shoulder motion for each 3D technique that was employed, the various tables provide the quantitative values that were obtained for the shoulder and wrist for both the initiation phase and the complete movement. These figures provide representative illustrations of the output provided by our analyses.

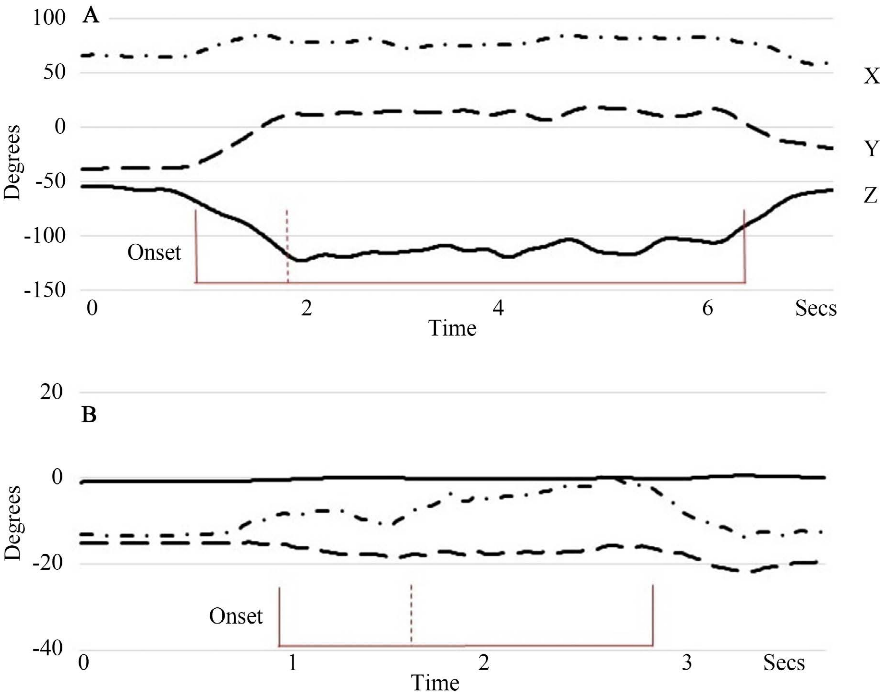


Figure 2. Exemplar shoulder waveforms in each dimension during a 'complete' 90˚ shoulder flexion with full elbow extension reach. The dashed red vertical line represents the end of the initiation phase. The first solid red line represents the beginning of the complete movement, while the rightmost red solid line represents the end of the complete movement. Panel A is data from P1 and Panel B from P2. Note that the onset and offsets are based on the motion of the hand, not on the motion of the represented joints. Also, note the differences in movement duration between the two participants (x-axis).

Table 2. Duration of movements in seconds by comparisons. Panel A is data from the complete movements while Panel B is data from the initiation phase of the complete movements. The P in second column's heading represents the participant number. U values indicate statistical testing was completed using the Mann-Whitney test.

A	Comparison	P	Mean (s) + SD	Median (s)	U value	Z score	P value
	All movements	1	3.13 (1.98)	2.70			

Continued

		2	1.21 (0.29)	1.11	290	6.24	0.000
	All right-hand movements	1	2.94 (2.45)	1.81			
		2	1.22 (0.33)	1.10	133	3.03	0.002
	All left-hand movements	1	3.32 (1.42)	3.21			
		2	1.20 (0.24)	1.14	10	5.72	0.000
	All 1st attempt movements	1	2.32 (1.68)	1.73			
		2	1.20 (0.29)	1.10	135	3.14	0.002
	All 2nd attempt movements	1	3.97 (1.94)	3.60			
		2	1.22 (0.29)	1.14	1	5.84	
	All open-ended movements	1	4.06 (2.22)	3.93			
		2	1.37 (0.25)	1.42	57	4.75	0.0000
	All goal-directed movements	1	2.16 (1.04)	2.12			
		2	1.06 (0.23)	1.02	80	4.16	0.0000
B	Comparison	P	Mean (s) + SD	Median (s)	U value	Z score	P value
	All movements	1	1.32 (0.54)	1.21			
		2	0.54 (0.13)	0.51	73	7.85	0.0000
	All right-hand movements	1	1.40 (0.54)	1.33			
		2	0.58 (0.15)	0.56	18	5.49	0.0000
	All left-hand movements	1	1.25 (0.54)	1.08			
		2	0.51 (0.11)	0.48	14.5	5.61	0.0000
	All 1st attempt movements	1	1.31 (0,54)	1.20			
		2	0.53 (0.14)	0.50	28.5	5.34	0.0000
	All 2nd attempt movements	1	1.33 (0.55)	1.25			
		2	0.56 (0.13)	0.51	7.5	5.70	0.0000
	All open-ended movements	1	1.49 (0.60)	1.43			
		2	0.62 (0.14)	0.57	8	5.76	0.0000
	All goal-directed movements	1	1.15 (0.42)	1.15			
		2	0.47 (0.08)	0.45	11	5.63	0.0000

Table 3. Peak hand velocity of the initiation phase. The units of all means and medians are in meters per second.

Comparison	P	Mean + 1SD	Median	U value	Z score	P value
All movements	1	7.03 (2.40)	6.71			
	2	12.09 (3.37)	11.39	147	7.30	0.0000
All right-hand movements	1	7.79 (2.87)	7.40			
	2	10.60 (2.11)	10.19	89	2.97	0.0000
All left-hand movements	1	6.30 (1.57)	6.48			
	2	13.58 (3.76)	12.65	5	5.83	0.0000
All 1st attempt movements	1	6.98 (2.16)	6.44			
	2	11.88 (3.25)	11.25	53	4.84	0.0000
All 2nd attempt movements	1	7.08 (2.67)	6.99			

Continued

	2	12.50 (3.49)	11.71	28	5.27	0.0000
All open-ended movements	1	6.81 (2.87)	6.29			
	2	12.88 (4.24)	11.61	40	5.10	0.0000
All goal-directed movements	1	7.26 (1.81)	7.08			
	2	11.30 (2.00)	10.95	30	5.22	0.0000

Table 4. 3D pathlength of the hand. Panel A is data from the complete movements while Panel B is data from the initiation phase of the complete movements. T values indicate statistical testing was completed using the t-test. Note the many non-significant results when the initiation phases of the data were compared.

A	Comparison	P	Mean + 1SD	Median	U value	Z score	P value
	All movements	1	1218 (594)	1176			
		2	636 (261)	540	351.5	5.78	0.0000
	All right-hand movements	1	1422 (657)	1367			
		2	582 (219)	519	38	5.05	0.0000
	All left-hand movements	1	1022 (458)	947			
		2	690 (292)	554	154	2.75	0.0059
	All 1st attempt movements	1	1326 (755)	1238			
		2	604 (271)	462	96	3.95	0.0000
	All 2nd attempt movements	1	1105 (340)	1101			
		2	667 (253)	557	74	4.29	0.0000
	All open-ended movements	1	1365 (656)	1311			
		2	785 (293)	907	117.5	3.51	0.0004
	All goal-directed movements	1	1064 (489)	997			
		2	486 (83)	499	47.5	4.85	0.0000

B	Comparison	P	Mean + 1SD	Median	T value	P value
	All movements	1	513 (195)	481		
		2	502 (233)	415	0.25	NS
	All right-hand movements	1	534 (178)	520		
		2	436 (210)	351	1.72	NS
	All left-hand movements	1	494 (212)	452		
		2	569 (240)	489	1.15	NS
	All 1st attempt movements	1	490 (172)	463		
		2	501 (233)	360	0.18	NS
	All 2nd attempt movements	1	538 (218)	481		
		2	504 (238)	438	0.51	NS
	All open-ended movements	1	474 (157)	452		
		2	629 (262)	746	-2.47	0.0171
	All goal-directed movements	1	554 (225)	532		
		2	376 (94)	342	3.58	0.0008

Figure 3 provides exemplar 3D hand trajectories for both participants during both the complete movements and initiation phases. This figure reflects that the participants primarily moved through different planes as they completed the movement. P1's trajectory magnitude was comparable to P2's during the initiation phase, albeit in a different plane, but the complete movement reflects significant extraneous motion.

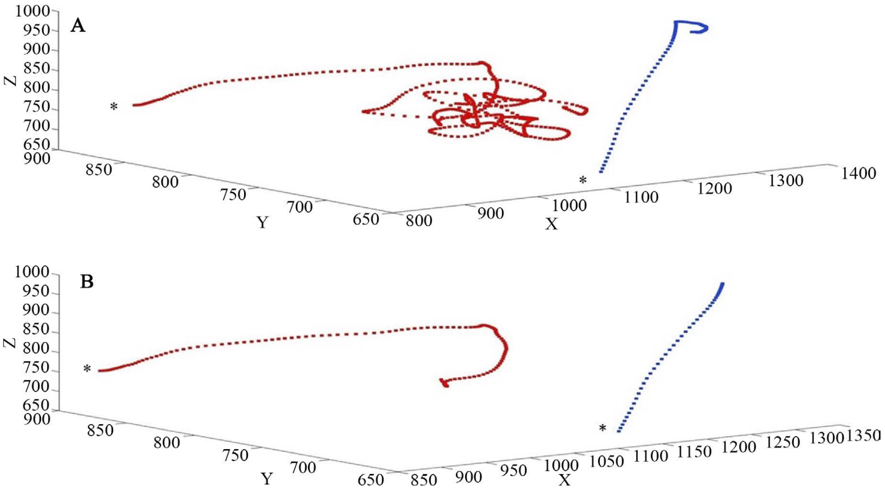
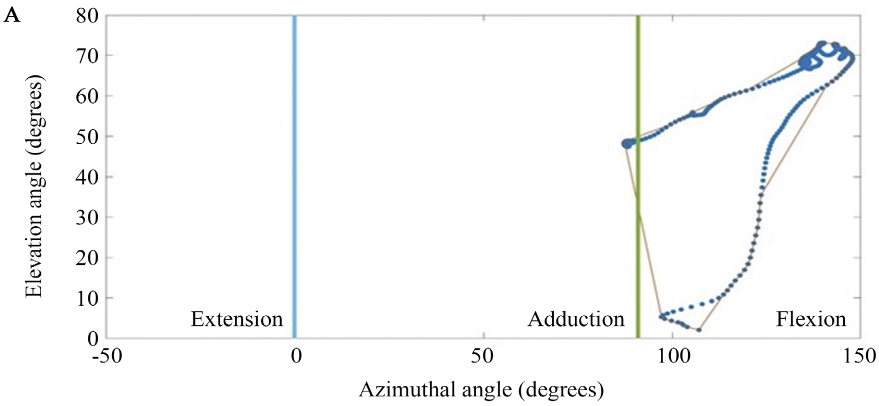


Figure 3. A 3D representation of the left hand during 90° shoulder flexion with full elbow extension reach. Data in red is P1, and blue represents P2. Panel A represents the complete movement and Panel B represents data from the initiation phase. *indicates first sample of initiation phase.

Figures 4 provides representative 3D area data of the shoulder for the complete movement. Panel A is data from P1, and Panel B is data from P2. The legend identifies which vertical lines represent particular motions. If the joint did not perform a particular motion during a given movement, the line representing that motion will not be seen on the graph. In Panel A, the right abscissa represents flexion. Panel A's trace reflects that the shoulder first moved with a combination of adduction and flexion (trace follows an upward and rightward trajectory), followed by a reversal reflecting movement toward extension (trace follows a leftward trajectory toward the blue line, passing into adduction). Panel B, which reflects P2's data, displays almost exclusively flexion.



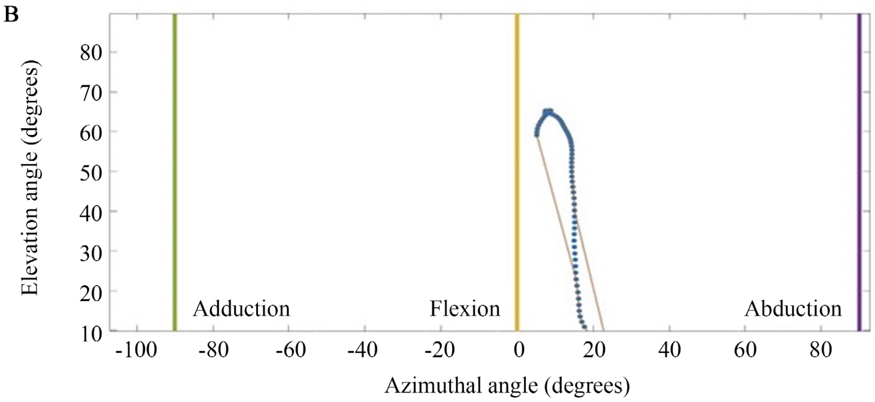


Figure 4. Exemplar 3D representation of the shoulder motion during a complete 90° shoulder flexion with full elbow extension reach. Panel A is data from P1 and Panel B from P2.

Table 5 and **Table 6** display the 3D areas of the complete movements and initiation phases of the shoulder and wrist. It can be observed that all comparisons reached statistical significance with the 3D areas of P1 being greater than P2's areas.

Table 5. Comparisons of Shoulder 3D Area in degrees^2. Panel A is data from the complete movements while Panel B is data from the initiation phase of the complete movements.

A	Comparison	P	Mean + 1SD	Median	U value	Z score	P value
	All movements	1	3560 (3286)	2504			
		2	1898 (2860)	491	549	4.30	0.0000
	All right-hand movements	1	4359 (3059)	2740			
		2	1934 (2804)	491	106	3.61	0.0003
	All left-hand movements	1	2890 (3419)	1686			
		2	1861(2975)	487	168	2.46	0.0139
	All 1st attempt movements	1	3915 (3422)	2718			
		2	2133 (3051)	373	152	2.79	0.0052
	All 2nd attempt movements	1	3189 (3271)	2013			
		2	1662 (2670)	551	125	3.20	0.0013
	All open-ended movements	1	4096 (3856)	2554			
		2	2783 (3433)	899	185	2.11	0.0349
	All goal-directed movements	1	3000 (2528)	2267			
		2	1013 (1815)	394	86	4.03	0.0000
B	**Comparison**	**P**	**Mean + 1SD**	**Median**	**U value**	**Z score**	**P value**
	All movements	1	2298 (2765)	1451			
		2	1523 (2507)	310	625	3.74	0.0001
	All right-hand movements	1	2310 (2277)	1738			
		2	1573 (2449)	336	144	2.80	0.0051

Continued

All left-hand movements	1	2285 (3215)	1053			
	2	1473 (2616)	304	169	2.44	0.0147
All 1st attempt movements	1	2385 (3080)	1455			
	2	1754 (2733)	255	172	2.38	0.0173
All 2nd attempt movements	1	2206 (2460)	1451			
	2	1292 (2294)	376	14.3	2.820	0.0048
All open-ended movements	1	2647 (3414)	1603			
	2	2242 (3042)	552	210	1.60	NS
All goal-directed movements	1	1933 (1878)	1334			
	2	804 (1585)	286	106	3.61	0.0003

Table 6. Wrist 3-D area comparisons in degrees^2. Panel A is data from the complete movements while Panel B is data from the initiation phase of the complete movements.

A	Comparison	P	Mean + 1SD	Median	U value	Z score	P value
	All movements	1	2584 (1801)	2051			
		2	844 (775)	529	332	5.92	0.0000
	All right-hand movements	1	2912 (1863)	2370			
		2	690 (582)	442	42	4.97	0.0000
	All left-hand movements	1	2269 (1719)	1610			
		2	998 (917)	613	131	3.23	0.0012
	All 1st attempt movements	1	2368 (1570)	1936			
		2	858 (732)	546	97	3.93	0.0000
	All 2nd attempt movements	1	2826 (1983)	2284			
		2	833 (817)	491	75	4.49	0.0000
	All open-ended movements	1	2880 (1889)	2284			
		2	1168 (933)	870	105	3.76	0.0001
	All goal-directed movements	1	2274 (1690)	1435			
		2	521 (374)	367	50	4.80	0.0000

B	Comparison	P	Mean + 1SD	Median	U value	Z score	P value
	All movements	1	1645 (1439)	1180			
		2	568 (541)	336	465.5	4.93	0.0000
	All right-hand movements	1	2067 (1801)	1660			
		2	572 (515)	369	109	3.54	0.0004
	All left-hand movements	1	1241 (831)	1060			
		2	564 (578)	324	122	3.41	0.0006
	All 1st attempt movements	1	1450 (1315)	1111			
		2	657 (641)	362	153	2.77	0.0056

Continued

All 2nd attempt movements	1	1848 (1561)	1621			
	2	480 (415)	316	88	3.99	0.0000
All open-ended movements	1	2021 (1737)	1376			
	2	752 (652)	537	139	3.06	0.0002
All goal-directed movements	1	1252 (927)	1044			
	2	385 (323)	296	92	3.91	0.0001

Table 7 displays that with only one exception, all of the comparisons between P1 and P2 for both the shoulder and wrist did not reach significance. This suggests that the participants may have utilized a similar movement strategy, despite significant differences in the absolute metrics of the measures (see Table 5 and Table 6).

Table 7. Initiation phase 3D area as a percentage of the 3D area of the Complete movement. Shoulder data is presented in Panel A and wrist data is presented in Panel B.

A	Comparison	P	Mean + 1SD	Median	T value	P value
	All movements	1	62 (25)	62		
		2	67 (23)	68	−1.09	NS
	All right-hand movements	1	53 (24)	56		
		2	70 (25)	73	−2.36	0.0227
	All left-hand movements	1	70 (22)	62		
		2	64 (20)	65	0.96	NS
	All 1st attempt movements	1	61 (25)	62		
		2	64 (22)	67	−0.48	NS
	All 2nd attempt movements	1	63 (24)	66		
		2	70 (24)	70	−1.04	NS
	All open-ended movements	1	56 (23)	61		
		2	70 (25)	71	−1.94	NS
	All goal-directed movements	1	67 (26)	75		
		2	64 (20)	65	0.44	NS

B	Comparison	P	Mean + 1SD	Median	T value	P value
	All movements	1	63 (26)	68		
		2	69 (23)	71	−1.12	NS
	All right-hand movements	1	65 (27)	69		
		2	77 (18)	78	−1.68	NS
	All left-hand movements	1	61 (26)	68		
		2	61 (25)	67	−0.02	NS
	All 1st attempt movements	1	63 (27)	68		

Continued

	2	73 (23)	71	−1.32	NS
All 2nd attempt movements	1	63 (26)	68		
	2	65 (23)	69	−0.26	NS
All open-ended movements	1	63 (25)	68		
	2	68 (27)	76	−0.62	NS
All goal-directed movements	1	63 (28)	68		
	2	70 (19)	70	−0.96	NS

3D jerk cost figures provide information about the magnitude of dimensionless jerk for each movement axis across a normalized (100%) movement duration. **Figure 5** provides exemplar data of jerk cost for the shoulder during a complete movement of a 90° shoulder flexion with full elbow extension reach. The data has been normalized to the peak velocity and duration of the movement, consistent with the recommendations of Balasubramanian, Melendez-Calderon and Burdet [9]. In this figure, Panel A represents data from P1, and Panel B represents data from P2. It can be observed that P1 displays significant jerk throughout the movement in the X and Z planes and in the Y plane around 60% and 95% of the movement. Conversely, P2 displays a brief 'spike' of jerk at about 50% of the movement in the Z plane. However, the X and Y planes display little jerk throughout any time during the movement. **Tables 8-10** provide information about the results of the 3D jerk analyses of the hand, shoulder and wrist movements.

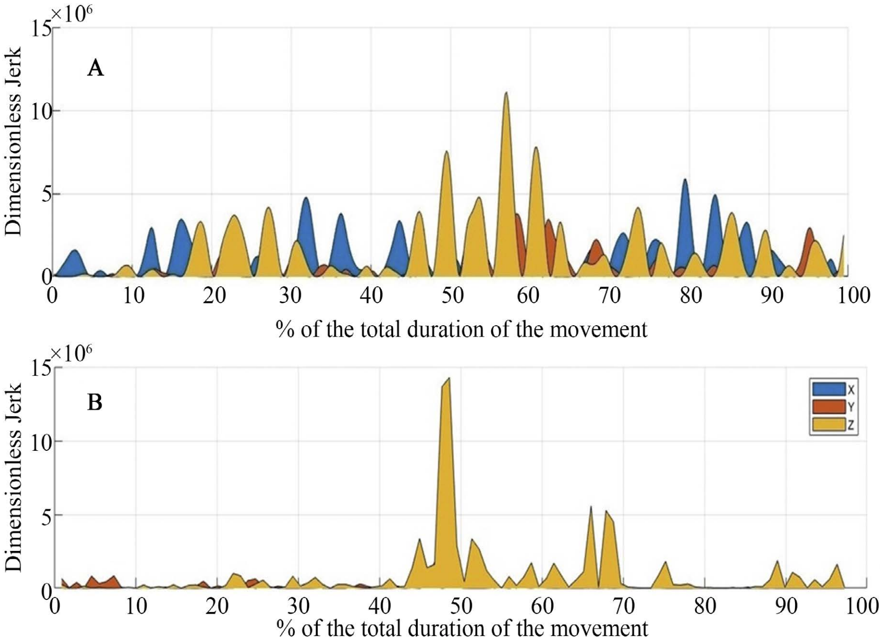


Figure 5. Jerk cost of the shoulder during a complete 90° shoulder flexion with full elbow extension reach. Panel A is data from P1 and Panel B from P2.

Table 8. Comparisons of hand 3D jerk cost (dimensionless) values. Panel A represents data from the complete movements while Panel B represents data from the initiation phase of the movements.

A	Comparison	P	Mean + 1SD	Median	T value	P score
	All movements	1	16.9 (2.4)	16.8		
		2	12.6 (1.8)	12.5	9.83	0.0000
	All right-hand movements	1	16.8 (2.9)	16.8		
		2	13.2 (1.9)	12.6	4.33	0.0000
	All left-hand movements	1	17.1 (1.9)	16.8		
		2	12.1 (1.4)	12.1	10.50	0.0000
	All 1st attempt movements	1	16.9 (2.7)	16.7		
		2	12.5 (1.9)	12.4	6.63	0.0000
	All 2nd attempt movements	1	16.8 (2.2)	16.9		
		2	12.7 (1.7)	12.5	7.23	0.0000
	All open-ended movements	1	16.1 (3.1)	16.3		
		2	13.4 (1.9)	13.0	4.33	0.0000
	All goal-directed movements	1	17.2 (1.5)	16.9		
		2	11.8 (1.2)	11.6	13.58	0.0000

B	Comparison	P	Mean + 1SD	Median	U value	Z score	P value
	All movements	1	12.8 (2.6)	13.0			
		2	9.7 (1.9)	9.4	384	5.53	0.0000
	All right-hand movements	1	11.9 (2.9)	11.4			
		2	10.5 (2.0)	10.1	189	1.84	0.0329
	All left-hand movements	1	13.7 (2.1)	13.9			
		2	8.8 (1.3)	8.7	22	5.47	0.0000
	All 1st attempt movements	1	12.7 (2.4)	12.8			
		2	9.5 (2.1)	9.2	88	4.11	0.0000
	All 2nd attempt movements	1	12.9 (2.9)	13.0			
		2	9.8 (1.8)	9.5	104	3.65	0.0003
	All open-ended movements	1	11.9 (3.0)	11.7			
		2	10.6 (2.1)	10.2	215	1.49	0.1362
	All goal-directed movements	1	13.8 (1.9)	13.7			
		2	8.8 (1.2)	8.7	3	5.80	0.0000

Table 9. Comparison of 3D shoulder jerk cost (dimensionless) values. Panel A represents data from the complete movements while Panel B represents data from the initiation phase of the movements.

A	Comparison	P	Mean + 1SD	Median	U value	Z score	P value
	All movements	1	17.6 (2.9)	17.7			
		2	14.1 (1.5)	13.8	313	6.06	0.0000
	All right-hand movements	1	16.9 (3.2)	17.0			

Continued

	2	14.3 (1.5)	14.0	123	3.25	0.0005
All left-hand movements	1	18.2 (2.4)	18.0			
	2	13.8 (1.6)	13.7	40	5.10	0.0000
All 1st attempt movements	1	17.7 (3.1)	17.6			
	2	13.9 (1.5)	13.8	71	4.46	0.0000
All 2nd attempt movements	1	17.4 (2.7)	17.7			
	2	14.2 (1.6)	14.0	87.5	4.00	0.0000
All open-ended movements	1	17.4 (3.9)	17.3			
	2	14.8 (1.6)	14.3	167	2.48	0.0066
All goal-directed movements	1	17.7 (1.4)	17.7			
	2	13.3 (1.1)	13.4	0	5.86	0.0000

B Comparison	P	Mean + 1SD	Median	U value	Z score	P value
All movements	1	13.4 (3.1)	14.2			
	2	10.8 (1.4)	10.6	513	4.57	0.0000
All right-hand movements	1	12.2 (3.0)	11.6			
	2	11.2 (1.4)	10.9	218	1.22	NS
All left-hand movements	1	14.6 (2.5)	15.5			
	2	10.3 (1.4)	10.4	56	4.77	0.0000
All 1st attempt movements	1	13.5 (3.3)	14.5			
	2	10.7 (1.5)	10.5	131	3.23	0.0006
All 2nd attempt movements	1	13.3 (2.9)	13.6			
	2	10.9 (1.4)	10.8	123	3.25	0.0006
All open-ended movements	1	12.5 (3.8)	11.5			
	2	11.3 (1.6)	11.1	258	0.61	0.2709
All goal-directed movements	1	14.3 (1.8)	14.7			
	2	10.2 (1.0)	10.4	5	5.76	0.0000

Table 10. Wrist 3D jerk cost (dimensionless) values. Panel A represents data from the complete movements while Panel B represents data from the initiation phase of the movements.

A Comparison	P	Mean + 1SD	Median	U value	Z score	P value
All movements	1	18.2 (2.8)	18.5			
	2	16.1 (1.3)	16.2	568	4.16	0.0000
All right-hand movements	1	17.7 (3.2)	17.9			
	2	16.0 (1.4)	15.9	171	2.22	0.0132
All left-hand movements	1	18.7 (2.4)	19.1			
	2	16.3 (1.2)	16.2	105	3.76	0.0000
All 1st attempt movements	1	18.3 (2.8)	18.6			
	2	16.0 (1.4)	16.0	123	3.39	0.0003

Continued

	All 2nd attempt movements	1	18.1 (2.9)	18.4			
		2	16.3 (1.2)	16.2	161	2.44	0.0073
	All open-ended movements	1	17.3 (3.6)	16.2			
		2	16.7 (1.4)	16.5	288	0.01	NS
	All goal-directed movements	1	19.1 (1.3)	18.8			
		2	15.6 (0.8)	15.8	0	5.86	0.0000
B	Comparison	P	Mean + 1SD	Median	U value	Z score	P value
	All movements	1	14.4 (3.0)	15.5			
		2	13.2 (1.3)	13.0	782	2.57	0.0050
	All right-hand movements	1	13.4 (2.8)	14.0			
		2	13.3 (1.4)	12.9	264.5	0.01	NS
	All left-hand movements	1	15.3 (3.0)	15.9			
		2	13.1 (1.2)	13.1	120	3.45	0.0002
	All 1st attempt movements	1	14.4 (3.1)	15.0			
		2	12.9 (1.4)	12.7	189	2.03	0.0211
	All 2nd attempt movements	1	14.4 (3.1)	15.5			
		2	13.5 (1.2)	13.4	200	1.61	NS
	All open-ended movements	1	12.9 (3.4)	11.5			
		2	13.9 (1.4)	13.7	221	1.37	NS
	All goal-directed movements	1	15.9 (1.5)	15.9			
		2	12.6 (0.8)	12.5	10	5.65	0.0000

4. Discussion

This investigation had two primary aims. The first aim was to characterize and quantify the arm movement patterns of an individual with NGLY1 Deficiency and compare those to patterns of an aged-matched neurotypical individual. The second aim was to introduce methodologies that can account for 3-dimensional arm movements spanning multiple planes of space. These methods are critical in this population, as the movements of individuals with NGLY1 Deficiency often preclude more traditional analyses focusing on a single plane of motion. We contend that these methodologies provide high fidelity information that, when paired with more traditional single dimensional measures, are more effective in not only characterizing the actions of individuals with NGLY1 Deficiency, but also in detecting subtle changes in movement resulting from pharmacological, genetic, or more traditional forms of physical therapy.

To gain insights into whether P1 had more or less difficulty with a given type of upper limb movement, if there were differences between the two hands, or if a second attempt of a movement differed from the first, the data were categorized into several different classes of movements. These categories are reflected in **Ta-**

ble 1. As mentioned in the Methods, due to the low success rate of P1 in picking up objects from a table, these data were not included in any statistical analyses. The success rate of P2 was not tabulated as, not surprisingly, she was able to complete all of the movements with no difficulty. Table 1 reflects the great difficulty P1 had performing movements that required her arms to cross the midline of her body. Additionally, although P1 was able to reach objects presented on a table directly in front of her, in most cases, she was unable to grasp the objects. We had speculated there may be a relationship between the size and shape of the object and her ability to pick up the various objects, but the data do not support that premise. Rather, P1's difficulty appears to revolve around her manual and digital fine motor control, which precluded her successful grasping of the objects.

On the other hand, when P1 was asked to grasp objects that were presented in the research assistant's hand in front of her, she had a much higher success rate. However, she still had marked difficulty with the golf ball and toy car, regardless of the object's presentation. It should be kept in mind that many of the objects she was asked to pick up from the table were the same as those she was able to grasp and remove from the research assistant's hand. She was fairly effective in grasping the pen from the research assistant but had no success picking the pen up from the table, regardless of the pen's orientation on the table. Table 1 suggests that it was not the object's themselves that presented the motor difficulties for P1, but rather the interaction between a particular object and the 'environment' the object was positioned in. Although we are not certain as to why our NGLY1 Deficient participant had more difficulty in grasping and picking objects up from the table, it could be that the addition of an object support system, *i.e.* the table, interfered with her ability to adequately plan and execute the fine motor control necessary to manipulate the hand such that it was in an adequate position to grasp and lift the object off of the table. Grasping the objects from the research assistant's hand allowed for a variety of ways for the participant's hand to approach the object. The use of the table reduced the number of functional hand orientations that would result in a successful grasp and lift motion. If substantiated with additional research, the concept of object presentation during tasks may be important for parents, caregivers, and therapists.

Table 2 reveals that P1 had significantly longer durations for both the complete movements as well as the initiation phases relative to P2. Table 3 shows that the peak hand velocity of P1 is significantly less than that of movements P2's movements, often by approaching 50%. These results are not unexpected, but Table 2 and Table 3 provide a quantitative means of expressing not only the magnitude of the actual values, but the statistical differences between the two participants as well.

Three-dimensional pathlength (PL) data provides a quantitative measure of the motions required across all three movements planes to complete a given task. As the hand is the end point of control for all of the movements, performed in this study, we calculated the hand's 3D PL (see **Figure 3**). **Table 4** provides evidence that, regardless of the comparisons, P1 always displayed greater PL than P2 during the complete movements. Interestingly, when comparing the 3D PLs of the two participants' initiation phases, many comparisons were not significantly different between P1 and P2. Although **Figure 3** displays hand trajectories (and not PL per se), the 3D data featured in the figure is what was used to calculate the 3D PL. This figure provides a clear representation of the differences in the complete hand movement trajectories (Panel A). Conversely, it can be observed that the differences during the initiation phase between P1 and P2 presented in Panel B are significantly less than those in Panel A. **Table 4** reveals that in addition to the lack of significant differences over all the collapsed categories, there are also no differences between the right and left hand or between the first and second attempt of the movements. However, when the data are instead grouped by movement category, **Table 4** does display significant differences during the initiation phase between P1 and P2. That is, both the open-ended and goal-directed comparisons reached significance, suggesting that grouping data based upon the goals of the task, can provide greater insights into the quality of the movements than if all movements are analyzed as a single group for each participant.

Table 5 and **Table 6** and **Figure 4** present data of the 3D area analyses. The tables reveal that all the comparisons with the exception of the initiation phase of the open-ended shoulder movements were significantly different between P1 and P2. These differences are also robust and consistent: P1's 3D areas were greater than those of P2. Considering P2's movements the neuro-typical participant as representative of coordinated, efficient movement patterns, the significantly greater 3D areas for P1's movements suggest a high level of uncoordinated and therefore inefficient, movement patterns. In particular, the differences present in the median values reflect a great amount of discoordination in P1's movements. These findings, and specifically the tables and **Figure 4**, highlight the value of using the 3D joint data to assess movement in this population. This measure provides unique quantitative information about the overall movement and, when combined with the knowledge of the actual joint trajectories obtained from the 3D area figures, enables investigators to begin to identify exactly how movement differs between a neuro-typical individual and one with NGLY1 Deficiency. Failing to use 3D non-linear measures may result in an incomplete characterization of the movement of NGLY1 patients. An incomplete characterization of movements potentially risks not being able to identify improvement (or regression) of movement patterns if only more traditional measures are used to assess movement. For example, traditional measures such as range of motion or peak angular velocity in a single plane of movement, while appropriate to characterize certain movements of neuro-typical individuals, will fail to completely characterize many movements of NGLY1 deficient patients. As mentioned previously, using 3D quantitative measures can aid in a full characterization of the difficulties experienced by individuals with extremely severe movements disorders. The fact that multiple movement planes are being simultaneously represented can provide clinicians with insights such as which movement plane an individual has the most difficulty with. Knowing this information would allow therapists to develop rehabilitation regimes designed to focus specifically on activities that can strengthen motions within that plane. Additionally, as genetic engineering becomes more prevalent, identifying subtle changes in movement can be better accomplished with 3D assessment techniques.

Jerk cost is a quantification of the smoothness of a movement. In this study, examinations of jerk cost across the shoulder, wrist and hand revealed a number of interesting differences between P1 and P2. First, an overwhelming majority of comparisons of jerk costs between the two participants were significantly different; further, in every single one of these instances, P2—the neuro-typical individual - exhibited greater smoothness of movement (*i.e.*, lower jerk cost) than P1 (see **Tables 8-10**). This suggests that jerk cost is a sensitive, robust measure of the movements of an individual with NGLY1 Deficiency. In particular, it appears to be able to quantify the differences in movement smoothness that are visually apparent in the 3D PL and area graphs between P1 and P2 (see **Figure 5**). Indeed, the jerk cost of a movement, as a complementary measure to 3D PL and area, allows an investigator to pinpoint not only the movement plane and boundaries as well as the time and duration of a movement, but also the quality of the movement itself.

The finding that 3D initiation area as a percentage of the complete movement was statistically indistinguishable between the participants, may suggest a similar underlying motor control strategy despite significant quantitative differences in our measures (**Table 7**). A series of elegant experiments in the early 1990’s by Cooke and Brown [12] [13] [14], explored the relationships between arm muscle activity and characteristics, and the temporal profile of a variety of arm movements. Their 1994 paper demonstrated measurable relationships between activation features, as represented by EMG, and temporal arm movement features. By modifying agonist and antagonist activity, acceleration and deceleration features could be modified to increase or decrease movement time. As a result of this foundational work, as well as research by other investigators in the 1970’s and 1980’s [15] [16], it has been suggested that the temporal features of movements are an important component of motor planning. Research in the area of the planning of arm movements currently continues [17] [18] often with more direct measurement of brain function than was provided by earlier investigations that relied on the use of EMG. The similarity in the proportional control of the initiation phase relative to the complete movement illustrated by our participants suggests the agonist and antagonist arm muscles may have functioned in a similar manner, despite vast differences in movement time. This may then suggest a similar underlying motor control strategy. Although this is speculative, and the current investigation did not obtain neuromuscular activation measures that would have provided additional insight into this possibility, the suggestion of common planning and control features between neurotypical and NGLY1 Deficient individuals is worthy of formal investigation.

The generalizability of the investigation is limited as it focuses on a single NGLY1 Deficiency patient. As with many syndromes resulting from genetic disorders, the range of movement behaviors can be quite large. Therefore, it is difficult to suggest P1's movements characterized in this report, can be considered as representative of all individuals with NGLY1 Deficiency. However, based on visual observation of other individuals with NGLY1 Deficiency, it appears likely that NGLY1 deficient patients will demonstrate movements across multiple anatomical planes, similar to those produced by P1, thereby reinforcing the need to assess movement using 3D techniques.

5. Conclusion

The current findings indicate there are significant differences between the arm movements of an individual with NGLY1-Deficiency and that of a healthy, aged-matched control. As P1 presented with many of the hyperkinetic movement difficulties typically associated with NGLY1 deficiency, these results were not unexpected; however, by assessing a relatively large variety of movements across several movement categories we were able to quantitatively and precisely describe the kinematics of each participant movements. Moreover, the use of several 3D data processing techniques enabled high-fidelity characterization and quantification of the movements. This was particularly important as P1 rarely performed the reaching movements within a primary plane of progression, instead moving through multiple planes while performing the motion (see 3D area tables and **Figure 4**). This multi-planar motion is also often reflected in the 3D jerk cost measures. Characterizing these movements using the above 3D measures and providing comparative data from a neurotypical participant provides a strong starting point for comparisons that may be useful to clinicians and therapists. Such knowledge can directly relate to both the assessment of the efficacy and the development of finely structured therapeutic interventions targeting specific phases and possibly, planes of motion, during a given movement. Future research will be conducted with an increased number of individuals with NGLY1 Deficiency, exploring the hand kinematics of the grasp itself, as well as investigating arm muscle activation patterns. These actions would increase the generalizability of results and provide additional insights into the impairments in fine motor control experienced by NGLY1 Deficient individuals.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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