KSA Longitudinal Study

Full dataset analysis

18.10.2021

Main input points

1. What to focus on in the analysis – towards a paper storyline – I've built a certain storyline for the ICORR presentation, does it make sense to keep it as base & expand from there?
   - How to structure it towards a paper storyline?
   - Current storyline: individual improvement motor / sensory, how do they change relative to each other / functional meaning

2. Main analysis T1 – T3 ? How to handle multiple measurements per subject (range 2 to 8)

3. Main messages so far:

- robotic method can capture improvement within subjects that are at ceiling of the clinical scale – especially for PM
- Changes in motor and sensory dissociated – are they really? Find other ways to quantify
- Proprioception important for functional hand use at discharge – but so is motor function to some extend (but statistically not sign.)

4. Last time we discussed other ways of quantifying change over time than t-test statistics → I calculated nr of subjects delta > SRD & nr of subjects that changed from impaired to less impaired – this is probably a good direction to look into those subjects individually, but the issue is that it's not that many subjects (according to robotic at least) – if e.g. it's only 3 subjects that changed above SRD in PM how conclusive whatever I find about them can be?

5. Last time we also talked about building a workflow in the analysis – not yet sure how to do that - so far looked into individual subjects simply in tables like see slide 18 to try to identify patterns which I could then try to statistically capture – would be helpful to discuss that again

Meeting 19.10.2021

1. Follow-up from last week
   - Fixing the modelling of factors contributing to change (H1)
   - H2: color-coding of subjects impaired at baseline, going deeper into that relationship, still not clear how to approach that with modelling
   - H3: we didn’t have time to discuss that

2. Discussion on therapy part of my project (prep. for progress meeting)

Research question and hypothesis

RQ: How do sensory and motor hand impairments evolve in sub-acute phase after stroke?

- H1: Both **improve**, given the spontaneous recovery window
  (Zandvliet et al. 2020)
- H2: Motor and proprioceptive recovery is **dissociated** in time and magnitude
  (Semrau et al. 2015)
- H3: Recovery of proprioception is a **pre-requisite** for full sensorimotor recovery
  (Zandvliet et al. 2020)

Participants information

- Recruited: 50
- At least one robotic measurement: 48
- At least two robotic measurements: 45 – report demographics for this group?
- Nr of subjects per session
- Age: 67.82 ± 10.53
- Gender: Females: 16, Males: 29
- Right handed: 42, Left handed: 3
- Right Hemispheric Stroke: 25, Left Hemispheric Stroke: 20
- Ischemic stroke: 34, Hemorrhagic stroke: 11
- Time since stroke: 34.38 ± 15.12

Min. weeks of stay	3	5	7	9	11	13	15
# of sessions	2	3	4	5	6	7	8
# of subjects	45	38	20	8	3	1	1

How to best treat these different timings in the analysis?
A: take fixed timeframe of 3 sessions (N=38)
B: take discharge time (N=45)

1. Better understand changes within each domain (motor / sensory)

H1: t-test & nr. of subjects impaired

Slide from ICORR 2021 + feedback from Achim & Thomas

N = 33, affected side

	Position Matching	AROM	Force Flex.	Velocity Ext.
T1	14.73 ± 5.28	50.49 ± 25.14	12.38 ± 12.50	166.32 ± 180.44
T3 (after 4 weeks)	12.83 ± 6.49	57.17 ± 24.59	14.96 ± 11.97	183.36 ± 177.26
paired t-test p-val.	**0.026**	**0.014**	**0.011**	0.33
Smallest Real Difference (SRD)	9.12	15.58	4.88	60.68
# Δ > SRD	3	5	10	12
# Δ to non-impaired	7	3	3	4

TO DO:

1. Update these values for total N available
2. Why does one group improve? Can we find some characteristics? Lesion location / neurophysiology? Time since stroke? Age?
   - But don't these questions go towards determining factors that contribute to improvement? **How do we define improvement in the first place?**
3. For this – organize all data in one place (check neurophysiology especially MEP)
4. Correlation with clinical changes for Thomas important as sanity check

Quantify the change – T1 vs T3 (full dataset)

N = 38, affected side

	Position Matching	AROM	Force Flex.	Velocity Ext.
T1	14.07 ± 5.44	50.22 ± 25.14	12.23 ± 12.19	164.98 ± 171.93
T3 (after 4 weeks)	12.22 ± 6.38	56.95 ± 23.26	15.00 ± 11.71	179.56 ± 170.05
paired t-test p-val.	**0.015**	**0.007**	**0.002**	0.343
Smallest Real Difference (SRD)	9.12	15.58	4.88	60.68
Imp. Threshold	10.63	63.20	10.93	255.6
# Δ > SRD	3	6	11	13
# Δ to non-impaired	8	3	4	5

How to get deeper from here?

- Did same subjects improve in all three modalities of motor tasks?
- Comparison to clinical changes
- Why did these subjects improve? Possible factors: lesion location, time since stroke, initial impairment – modelling?

Compare to clinical changes

N = 37, affected side

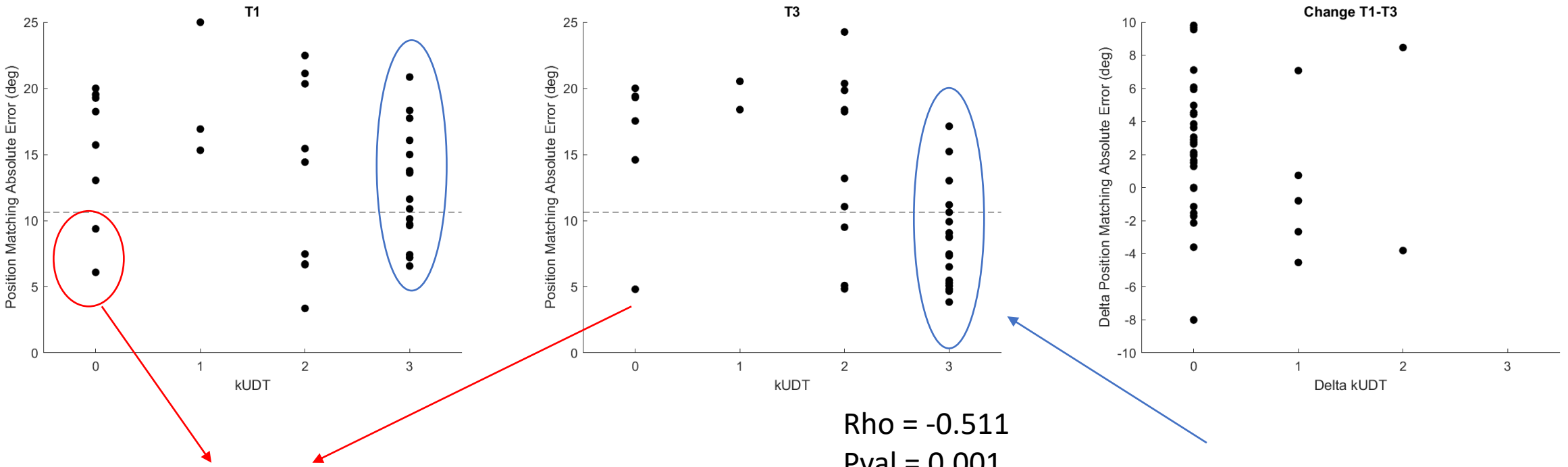
	kUDT	FMA Motor	FMA Hand	BBT Aff.	BBT L. Aff.
T1	1.86 ± 1.23	30.41 ± 23.44	6.03 ± 5.85	17.35 ± 19.04	48.62 ± 10.39
T3 (after 4 weeks)	2.11 ± 1.10	36.95 ± 22.66	7.73 ± 5.82	23.27 ± 23.23	56.05 ± 9.91
paired t-test p-val.	**0.011**	**2.10e-08**	**6.15e-05**	**3.03e-05**	**3.59e-07**
MDC	1	5.2	2?	5.5	5.5
Imp. threshold	3	60	14	54.3	54.3
# Δ > MDC	7	21	14	17	24
# Δ to non-impaired	2	7	4	4	10

Generally changes more significant and a higher number of subjects improved > MDC than in robotic

Somatosensory / Motor Evoked Potentials (SSEP / MEP)

Position matching vs kUDT

N=37



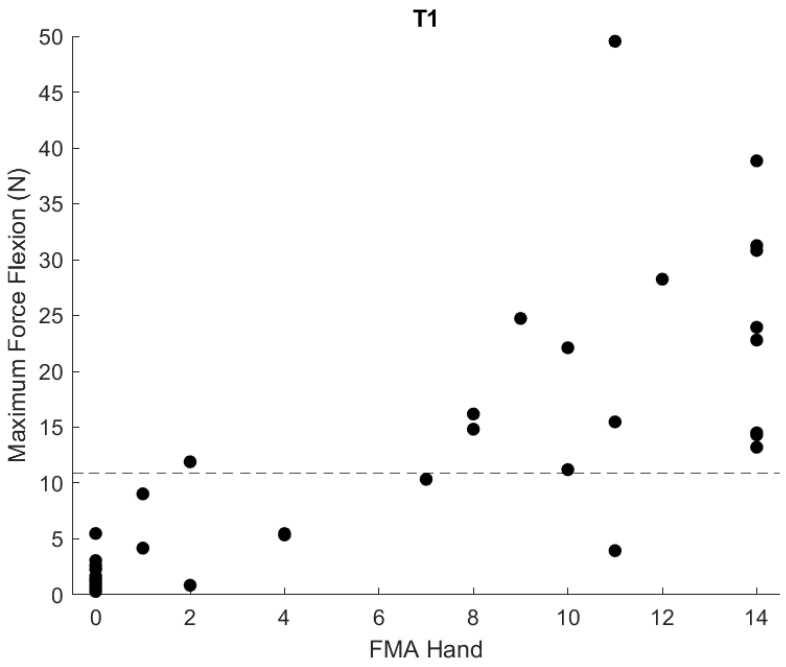
Rho = -0.511
Pval = 0.001

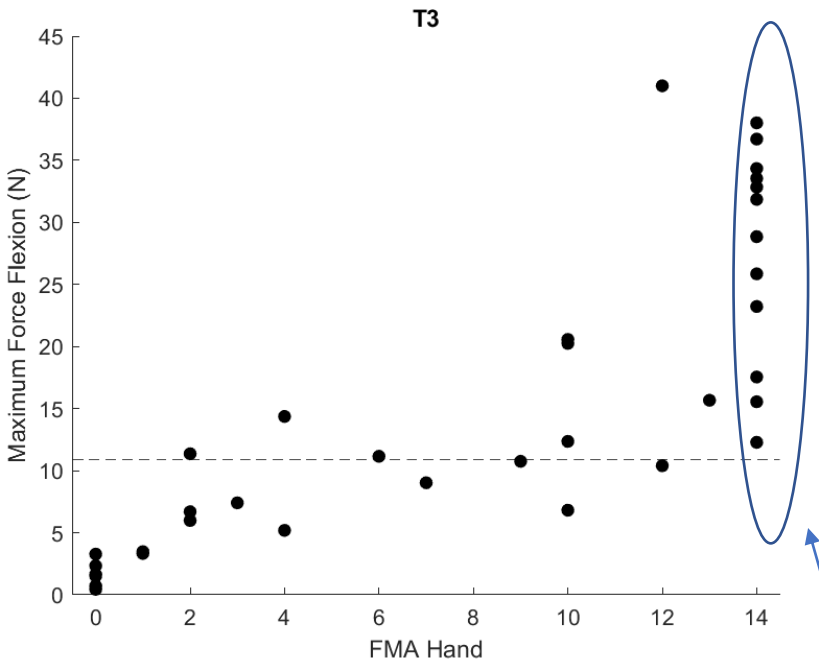
- S22 (kUDT: 0 at inclusion and discharge) – good hand function overall, FM Hand = 14, good cognitively (MoCA 28,29)
- S28 improved to 2 kUDT but decreased in PM to 13 (below impairment threshold)

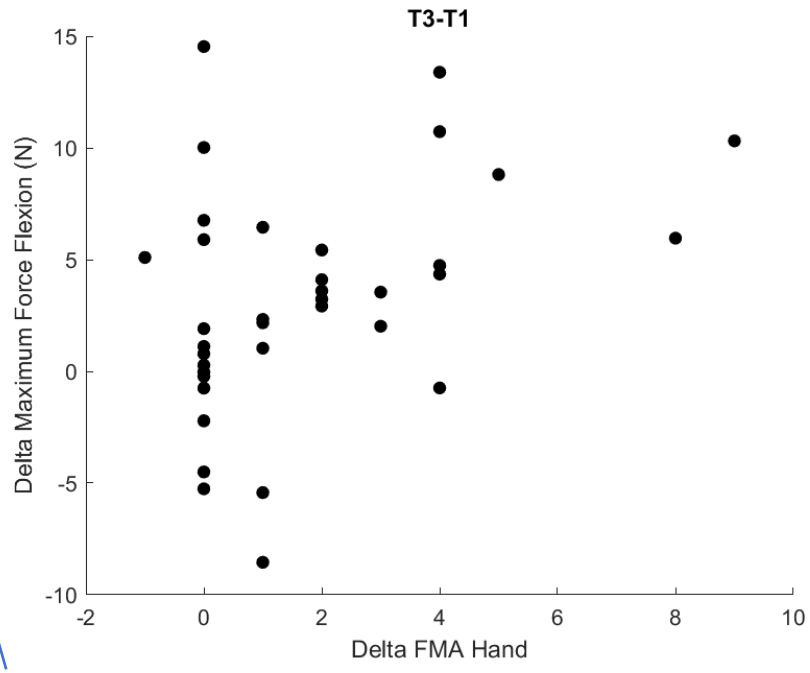
Most subjects that improved in PM were in ceiling of kUDT (we can see how this group moved down towards smaller PM error)

Max Force Flex vs FMA

N=37







Rho = 0.848
P-val = 3.55e-11

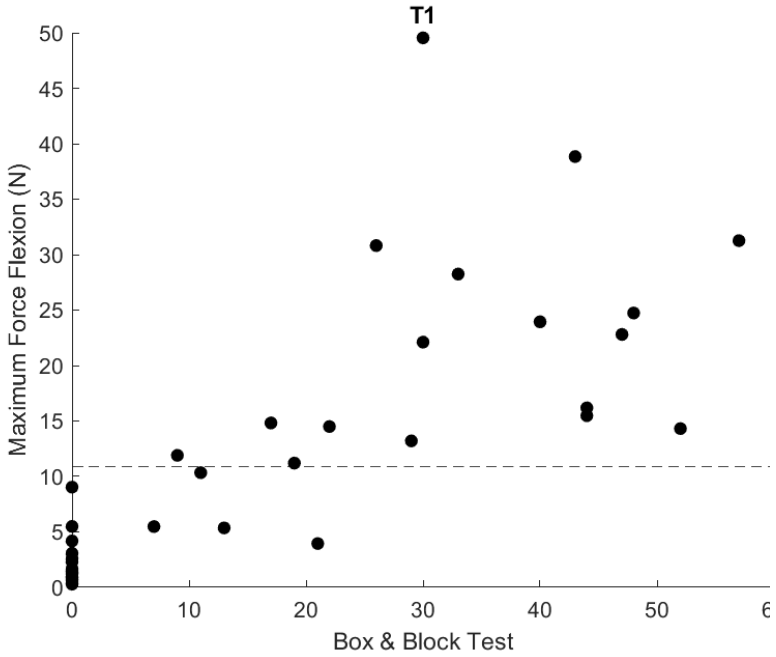
Rho = 0.896
P-val = 6.41e-14

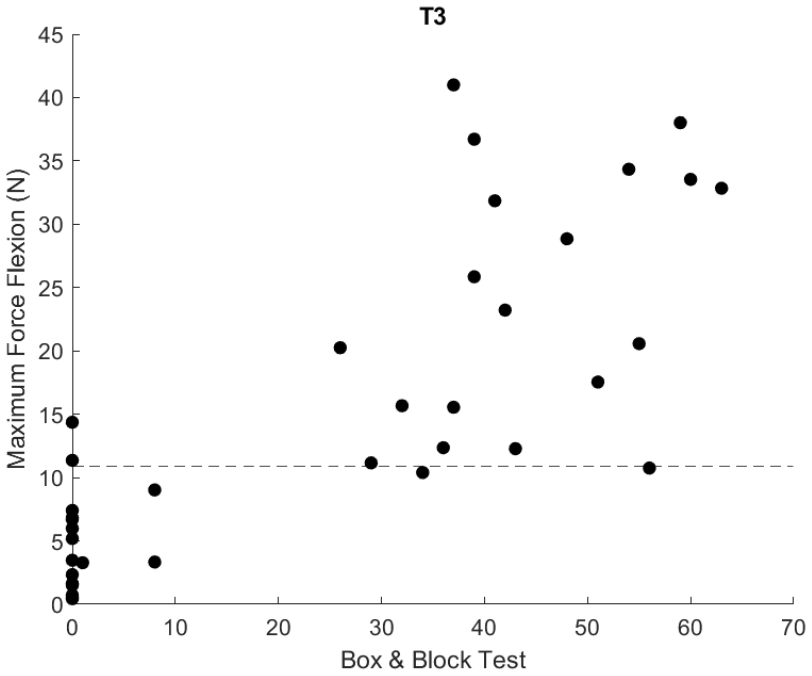
This group grew over time and the relationship between the two became stronger

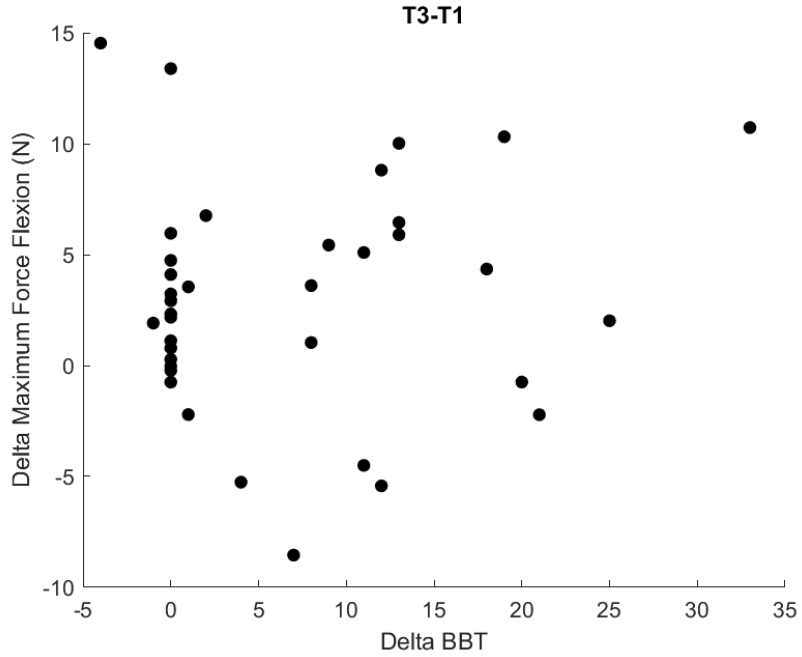
Rho = 0.399
P-val = 0.014
*not Bonferroni corrected

PM vs BBT & Force vs BBT

This is more in the direction of H3



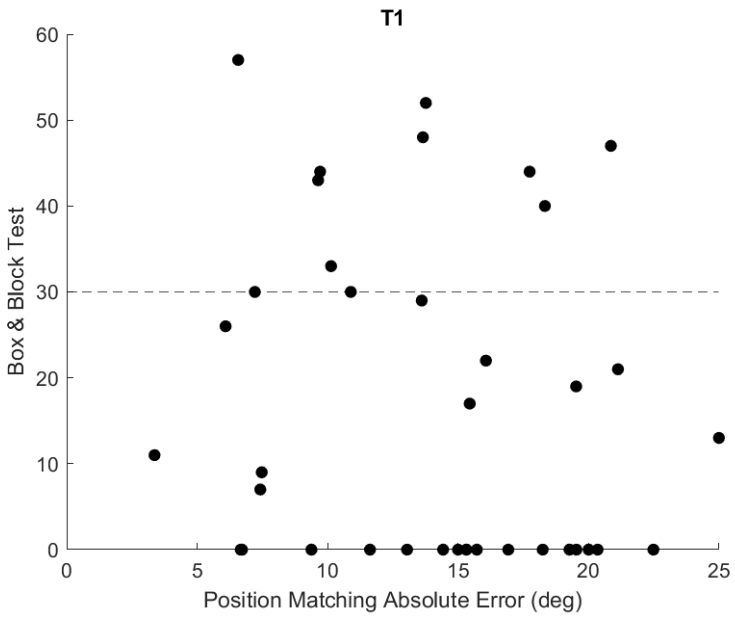


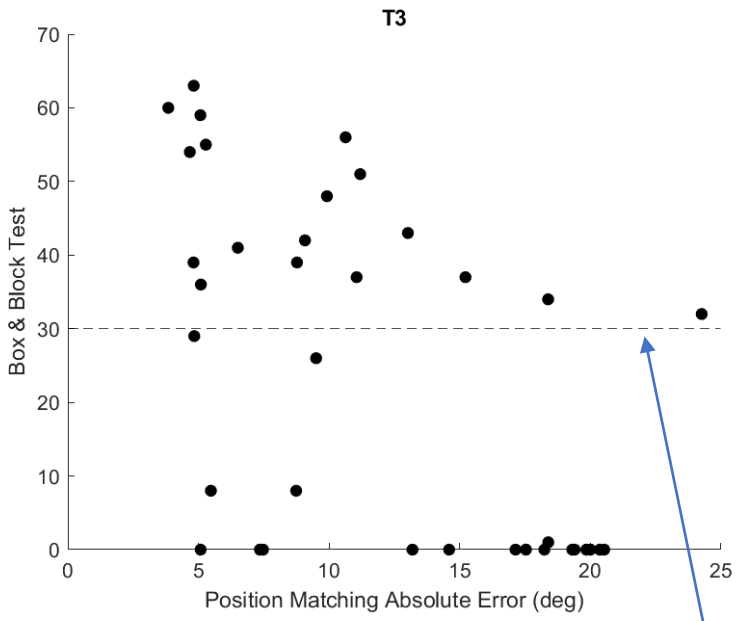


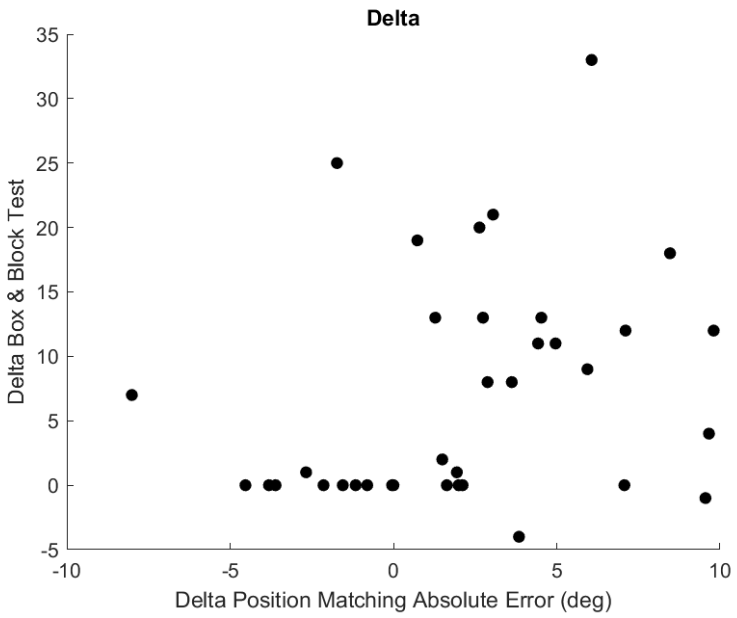
N=37

PM vs BBT & Force vs BBT

N=37







Functional hand use threshold in BBT

What about neurophysiology

- Especially important for PM because we don’t see clear results when comparing to KUDT
- Not fully analyzed yet

Effect of initial impairment & time since stroke on recovery

- Delta PM ~ 1 + TimeSinceStroke + Initial Impairment + (1 | Subject)

Model information:

Number of observations	37
Fixed effects coefficients	3
Random effects coefficients	37
Covariance parameters	2

Formula:

y ~ 1 + initialPM + TimeSinceStrokeAtT1 + (1 | Subject)

Model fit statistics:

AIC	BIC	LogLikelihood	Deviance
217.6	225.66	-103.8	207.6

Fixed effects coefficients (95% CIs):

Name	Estimate	SE	tStat	DF	pValue	Lower	Upper
'(Intercept)'	0.29909	1.976	0.15136	34	0.88058	-3.7166	4.3148
'initialPM'	0.22279	0.13872	1.606	34	0.11753	-0.059137	0.50471
'TimeSinceStrokeAtT1'	-0.036549	0.049175	-0.74324	34	0.46244	-0.13649	0.063387

Correction: Effect of initial impairment & time since stroke on recovery - proprioception

- Delta PM ~ 1 + TimeSinceStroke + baseline kUDT

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Linear mixed-effects model fit by ML

Model information:
    Number of observations             37
    Fixed effects coefficients          3
    Random effects coefficients         0
    Covariance parameters               1

Formula:
    y ~ 1 + baselinekUDT + TimeSinceStrokeAtT1

Model fit statistics:
    AIC       BIC       LogLikelihood    Deviance
    211.27    217.71    -101.63          203.27

Fixed effects coefficients (95% CIs):
    Name                      Estimate     SE          tStat       DF    pValue       Lower        Upper
    '(Intercept)'               -0.7488      1.8549    -0.40368    34      0.68898     -4.5185      3.0209
    'baselinekUDT'               1.404       0.5128     2.7379     34    0.0097671     0.36186     2.4461
    'TimeSinceStrokeAtT1'     0.0081494    0.040638     0.20054    34      0.84226    -0.074437    0.090736

Random effects covariance parameters (95% CIs):
Group: Error
    Name            Estimate    Lower     Upper
    'Res Std'       3.7733      3.0045    4.7388
```

Correction: Effect of initial impairment & time since stroke on recovery – motor

- Delta Force ~ 1 + TimeSinceStroke + baseline FMA Hand

```
Linear mixed-effects model fit by ML

Model information:
    Number of observations             37
    Fixed effects coefficients          3
    Random effects coefficients         0
    Covariance parameters               1

Formula:
    y ~ 1 + baselineFMAH + TimeSinceStrokeAtT1

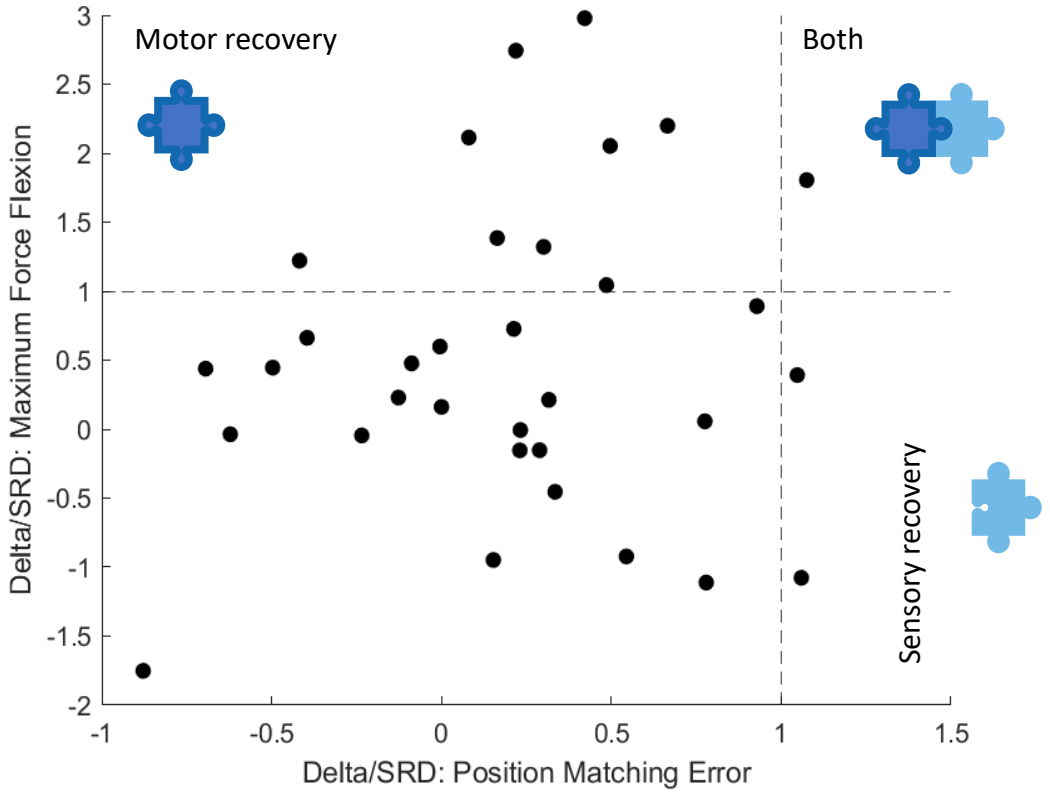
Model fit statistics:
    AIC       BIC       LogLikelihood    Deviance
    232.27    238.72    -112.14          224.27

Fixed effects coefficients (95% CIs):
    Name                      Estimate     SE          tStat       DF    pValue      Lower       Upper
    '(Intercept)'                3.9987      2.3177      1.7253     34    0.093558    -0.71147     8.7089
    'baselineFMAH'              0.067641     0.14391     0.47002    34     0.64134    -0.22482     0.3601
    'TimeSinceStrokeAtT1'       -0.040083    0.054288    -0.73833   34     0.46538    -0.15041    0.070244

Random effects covariance parameters (95% CIs):
Group: Error
    Name             Estimate    Lower     Upper
    'Res Std'        5.0117      3.9906    6.2941
```

2. Understanding how the changes interact

H2: correlation between delta motor /delta sensory



Slide from ICORR 2021 + feedback from Achim & Thomas

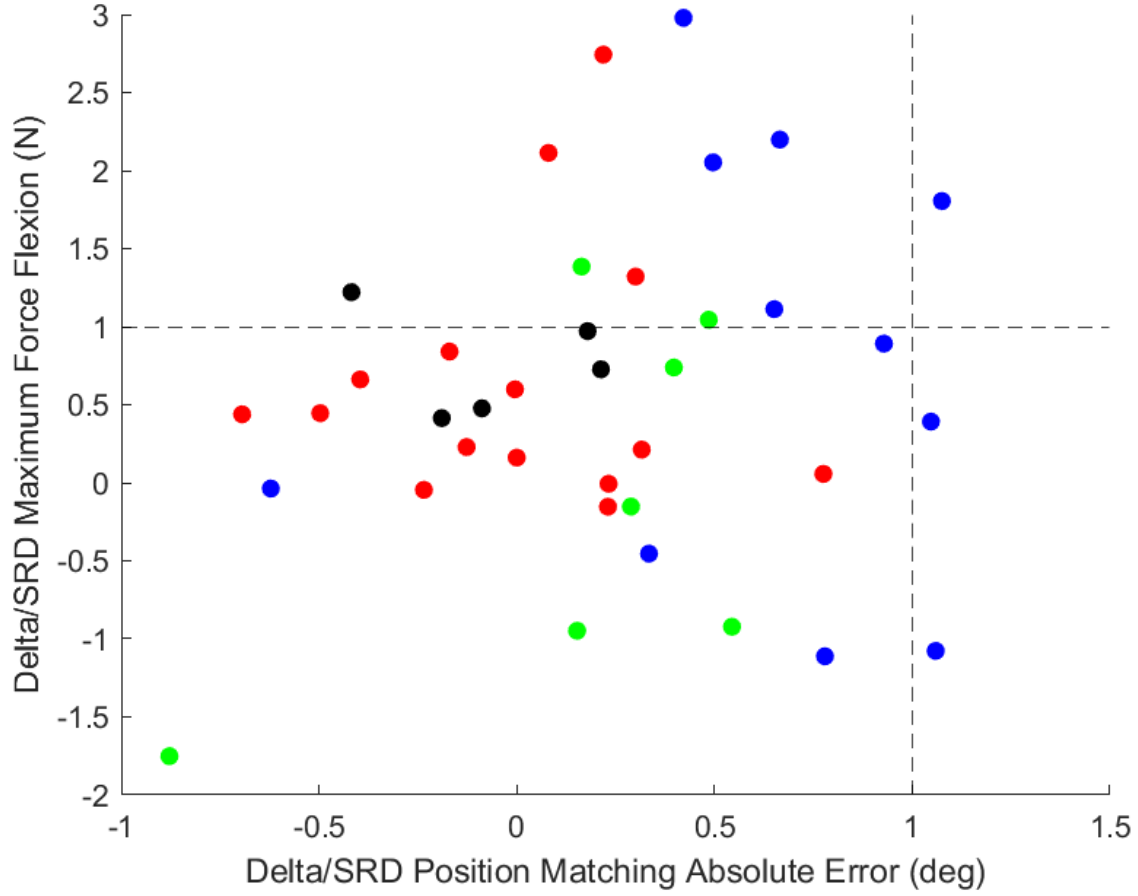
TO DO:

1. Repeat the analysis with all the data I have
2. This analysis doesn't include e.g. aspect of how many subjects change from impaired to not impaired
3. Important to take into account the initial impairment into this analysis
   - Or maybe this should be part of H1

   Important to clearly define improvement / recovery – check how it's done in Semrau and other work with robotic metrics

4. For Thomas it was not clear why motor and sensory are dissociated, doesn't intuitively make sense.

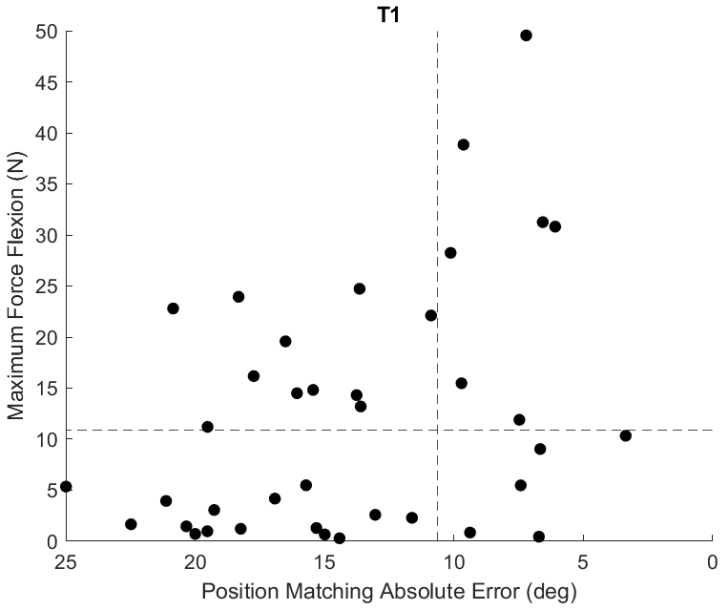
Color-coding of subjects based on baseline impairment



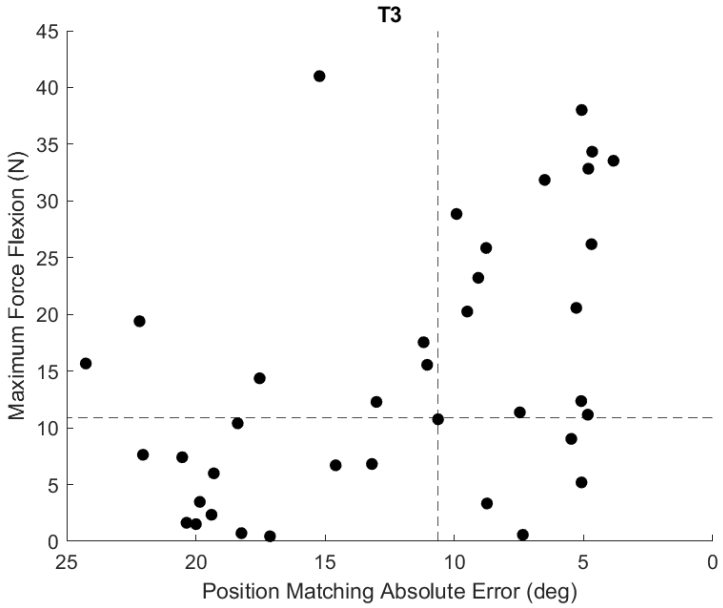
- Blue- sensory only impaired at T1
- Black – only motor impaired at T1
- Red – both impaired at T1
- Green – none impaired at T1

How to best capture this relationship?

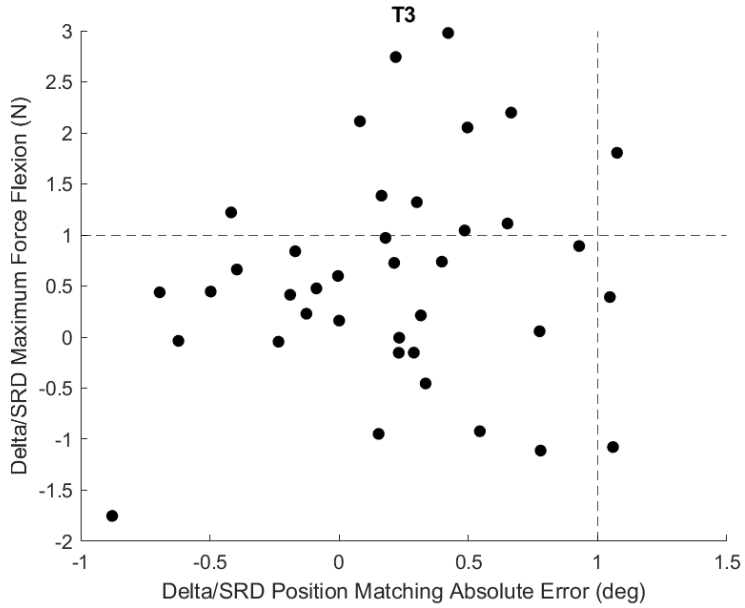
N=38



Rho = -0.300
P-val = 0.067

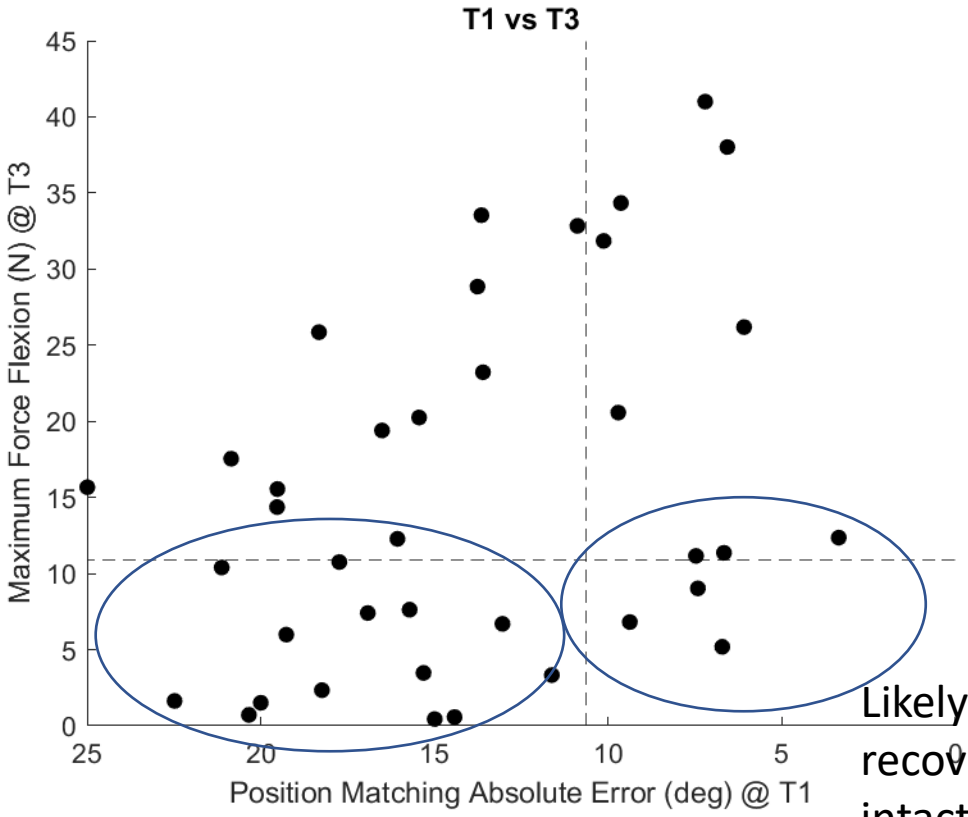


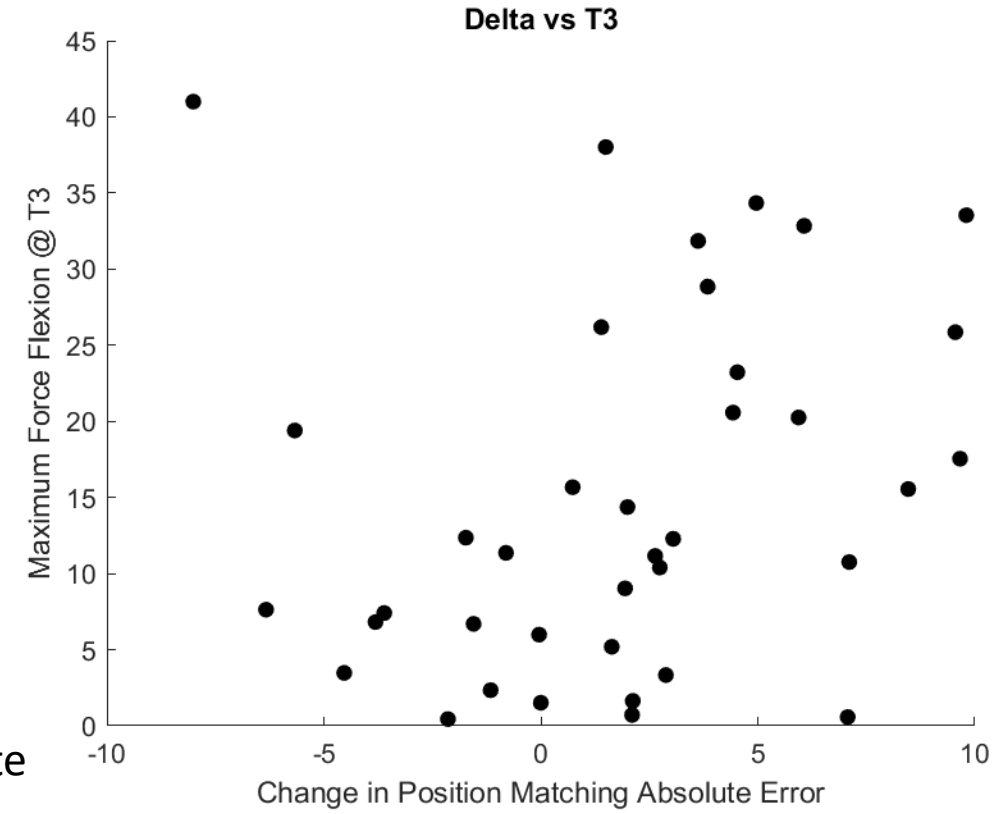
Rho = -0.482
P-val = 0.002



Rho = 0.112
P-val = 0.503

Looking deeper into the relationship

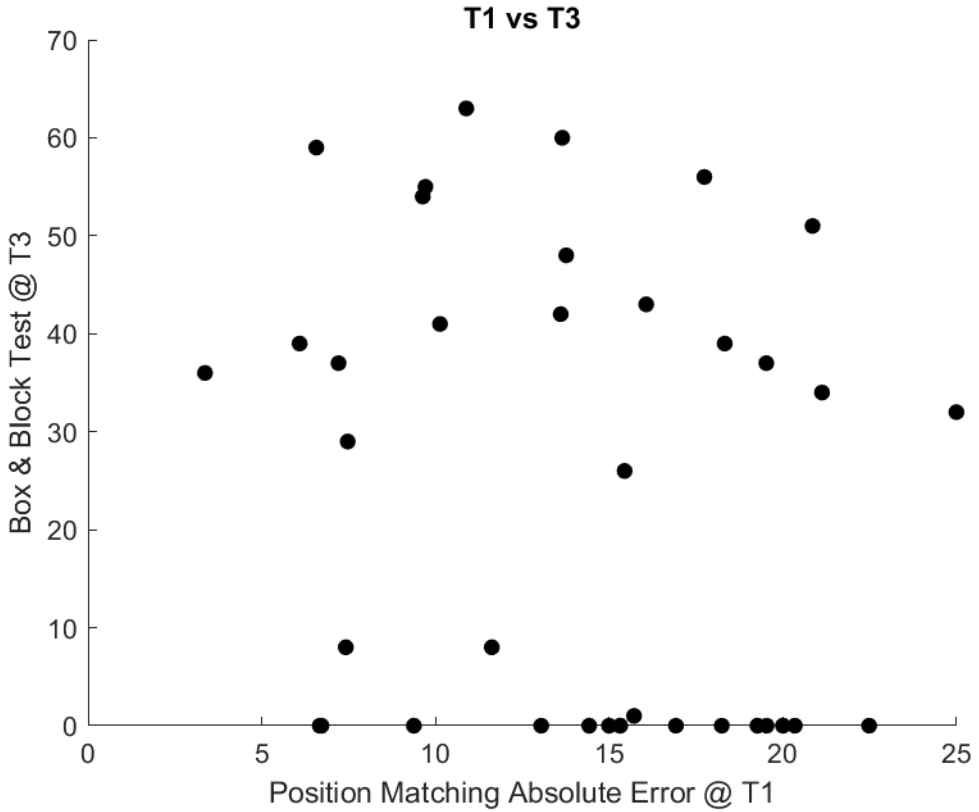


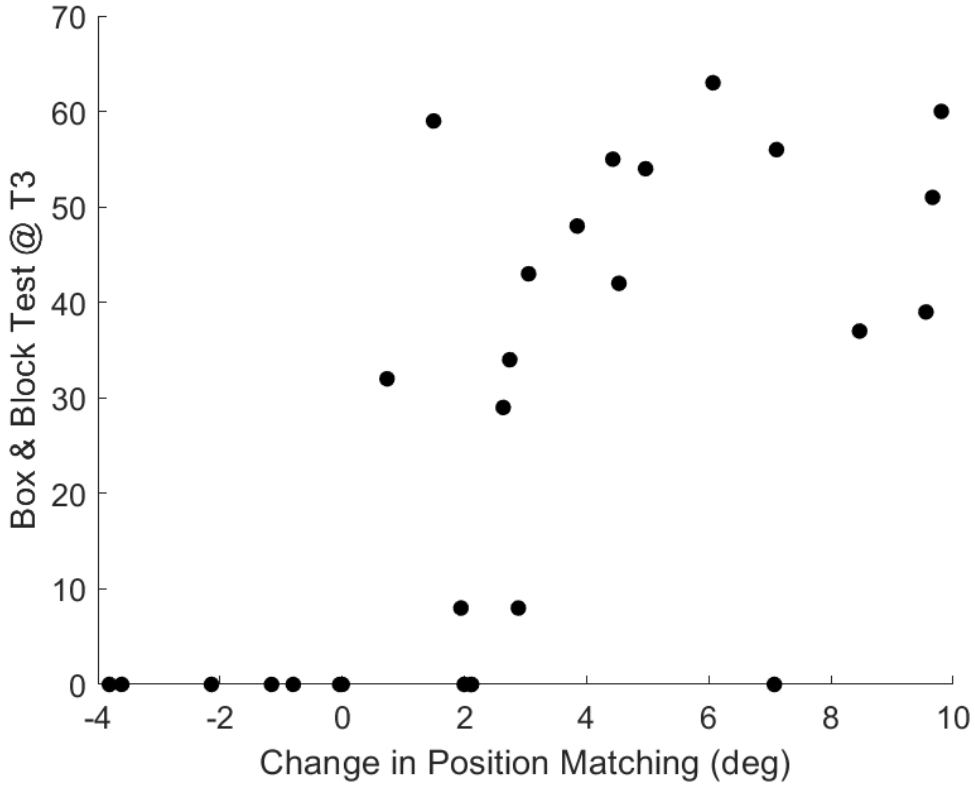


Likely did not recover despite intact proprioception?

Is baseline PM a requirement for recovered force at discharge?

Similar observations in BBT





Modelling approach

- delta AROM ~ 1 + delta PM + baseline FMA

Formula:

```
y ~ 1 + Sensory + baselineFMA + (1 | Subject)
```

Model fit statistics:

AIC	BIC	LogLikelihood	Deviance
309.97	318.03	-149.99	299.97

Fixed effects coefficients (95% CIs):

Name	Estimate	SE	tStat	DF	pValue	Lower	Upper
'(Intercept)'	9.9751	3.8428	2.5958	34	0.013836	2.1656	17.785
'Sensory'	-0.58326	0.67657	-0.86207	34	0.39469	-1.9582	0.7917
'baselineFMA'	-0.055005	0.12108	-0.45428	34	0.65251	-0.30107	0.19106

Delta itself should contain already the info about starting level somehow

Looking into individual subjects

	PM				Max Force		
	S1	S3	Diff		S1	S3	Diff
2	13.04248	14.59264	-1.55015	2	2.594065	6.69608	4.102015
4	6.570178	5.074501	1.495676	4	31.25777	38.01637	6.758602
5	24.99255	24.25927	0.73328	5	5.358545	15.67242	10.31387
6	14.99341	17.13361	-2.1402	6	0.664288	0.442122	-0.22217
7	19.52107	11.05336	8.467713	7	11.20374	15.55325	4.34951
8	17.73889	10.63169	7.107194	8	16.18104	10.75611	-5.42493
11	19.26573	19.3065	-0.04077	11	3.067872	5.988944	2.921072
12	15.71521	22.04814	-6.33294	12	5.48907	7.627785	2.138715
13	13.76235	9.917303	3.845046	13	14.31607	28.84971	14.53364
14	13.64854	3.843934	9.804603	14	24.73362	33.54162	8.807995
16	16.92032	20.5292	-3.60888	16	4.179925	7.409285	3.22936
17	19.52982	17.53278	1.997038	17	0.983769	14.36862	13.38485
18	22.481	20.36315	2.117852	18	1.664194	1.633071	-0.03112
19	20	20	0	19	0.726801	1.513366	0.786564
20	7.418833	5.476446	1.942387	20	5.480427	9.026317	3.54589
21	14.42273	7.351166	7.071565	21	0.296413	0.573297	0.276884
22	6.089466	4.696273	1.393193	22	30.81571	26.18796	-4.62774
24	20.3413	18.23788	2.	24	1.464713	0.715151	-0.74956
25	18.24004	19.39687	-1.15683	25	1.223806	2.340578	1.116772
26	13.60418	9.075637	4.528543	26	13.20659	23.22349	10.01689
27	16.06547	13.01531	3.05016	27	14.49924	12.2821	-2.21714
28	9.378522	13.18972	-3.8112	28	0.85532	6.814596	5.959275
29	9.710914	5.282768	4.428146	29	15.4772	20.57271	5.095515
30	7.209461	15.21876	-8.0093	30	49.54504	40.99915	-8.54588
31	11.62179	8.739306	2.882488	31	2.298618	3.334512	1.035894
34	18.32433	8.771181	9.553144	34	23.94403	25.85599	1.911966
35	21.12457	18.38316	2.741416	35	3.951405	10.39882	6.447415
36	10.88624	4.818303	6.067934	36	22.11265	32.84091	10.72826
39	16.50951	22.18045	-5.67094	39	19.57936	19.39756	-0.1818
41	20.85217	11.19071	9.661458	41	22.8011	17.54442	-5.25669
42	6.667053	7.46895	-0.8019	42	9.036088	11.36233	2.326243
43	9.633233	4.669022	4.964211	43	38.84154	34.34	-4.50155
44	7.473626	4.839239	2.634388	44	11.90356	11.16004	-0.74353
45	15.31637	19.84757	-4.5312	45	1.30013	3.474616	2.174486
46	6.717157	5.08258	1.634577	46	0.449522	5.189693	4.740171
47	15.44307	9.503177	5.939889	47	14.82285	20.25186	5.429016
49	10.1312	6.506886	3.624316	49	28.24802	31.85131	3.603285
50	3.36547	5.093026	-1.72756	50	10.33829	12.35879	2.020493

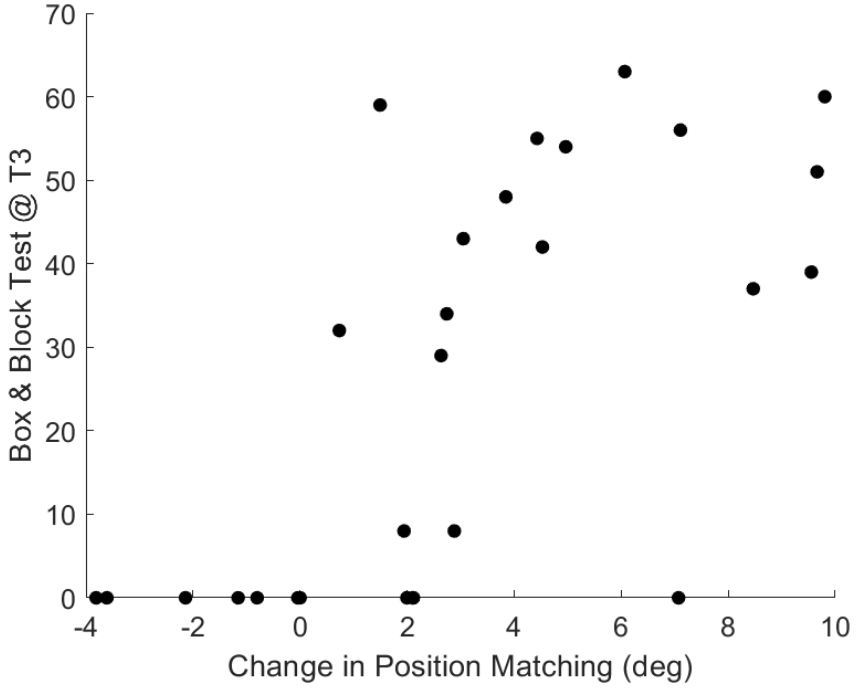
only impaired subjects at baseline in both domains

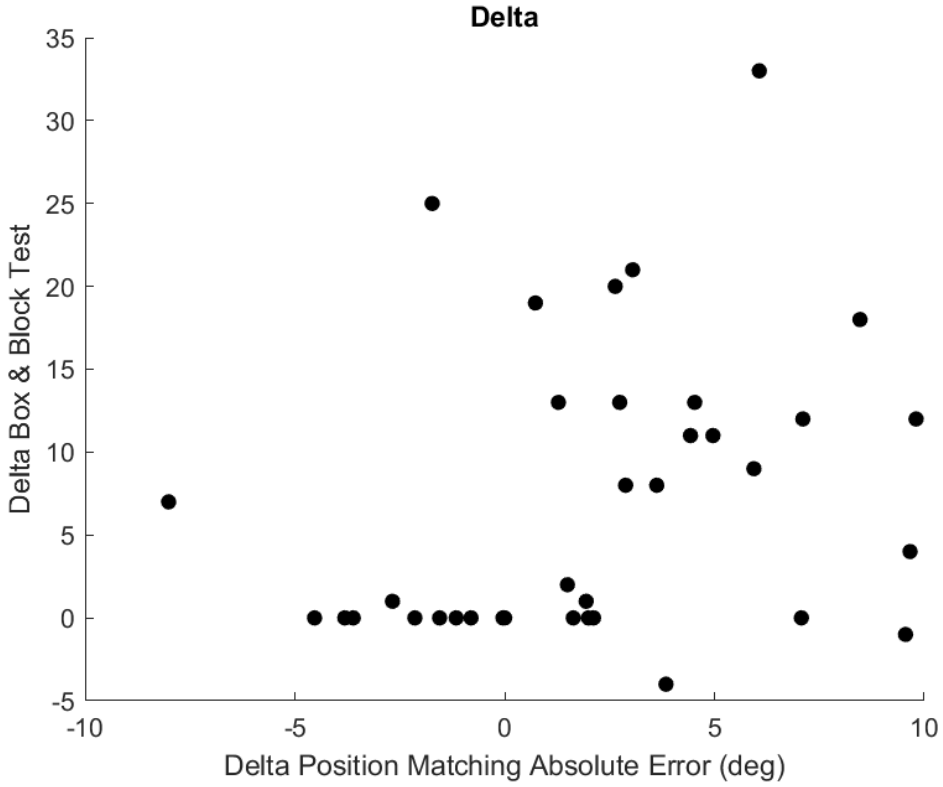
	PM			Tot sessions		Max Force		
	S1	S3	Diff			S1	S3	Diff
2	13.04248	14.59264	-1.55015	4	2	2.594065	6.69608	4.102015
5	24.99255	24.25927	0.73328	3	5	5.358545	15.67242	10.31387
6	14.99341	17.13361	-2.1402	6	6	0.664288	0.442122	-0.22217
11	19.26573	19.3065	-0.04077	5	11	3.067872	5.988944	2.921072
12	15.71521	22.04814	-6.33294	3	12	5.48907	7.627785	2.138715
16	16.92032	20.5292	-3.60888	5	16	4.179925	7.409285	3.22936
17	19.52982	17.53278	1.997038	3	17	0.983769	14.36862	13.38485
18	22.481	20.36315	2.117852	4	18	1.664194	1.633071	-0.03112
19	20	20	0	8	19	0.726801	1.513366	0.786564
21	14.42273	7.351166	7.071565	3	21	0.296413	0.573297	0.276884
24	20.3413	18.23788	2.103423	4	24	1.464713	0.715151	-0.74956
25	18.24004	19.39687	-1.15683	5	25	1.223806	2.340578	1.116772
31	11.62179	8.739306	2.882488	4	31	2.298618	3.334512	1.035894
35	21.12457	18.38316	2.741416	3	35	3.951405	10.39882	6.447415
45	15.31637	19.84757	-4.5312	5	45	1.30013	3.474616	2.174486

Subjects impaired in both domains generally did not improve significantly within 4 weeks. A few that did, only improved in one aspect (sensory or motor)

3. Impact of those changes on functional hand use

H3: change in proprioception vs functional hand use





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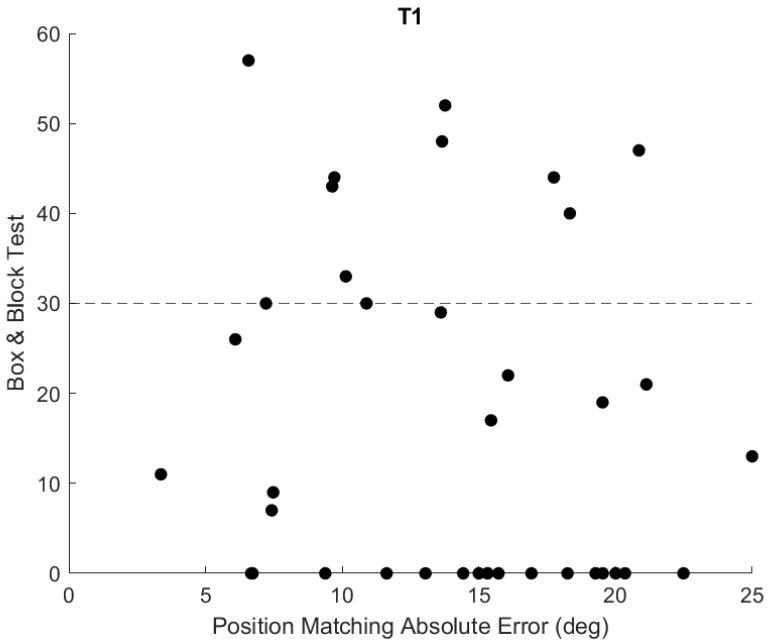
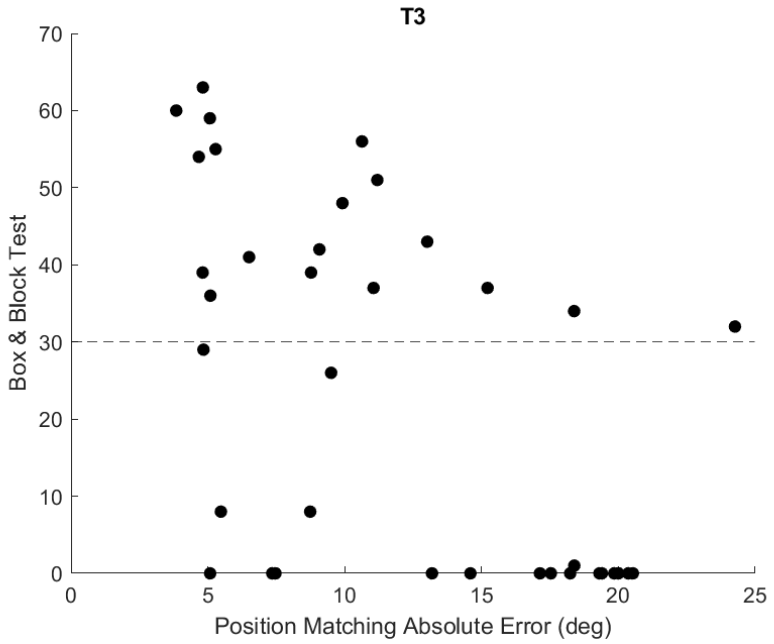

T1
Box & Block Test
Position Matching Absolute Error (deg)
0
10
20
30
40
50
60
0
5
10
15
20
25


T3
Box & Block Test
Position Matching Absolute Error (deg)
0
10
20
30
40
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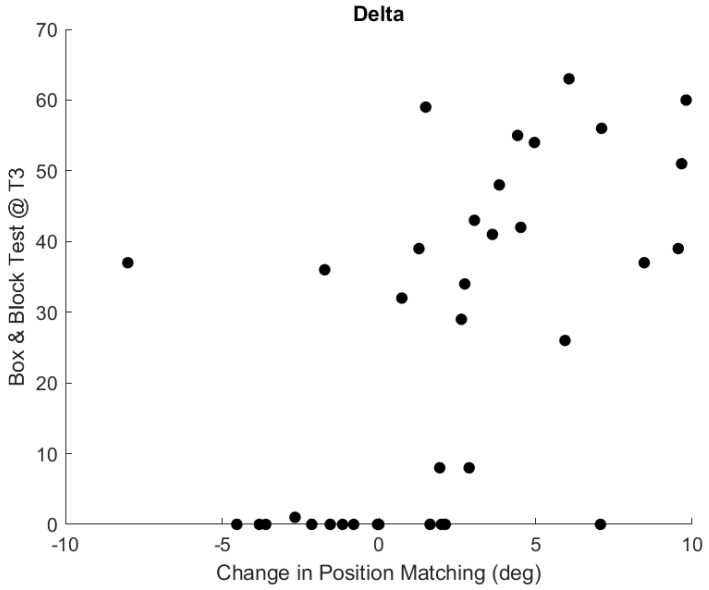
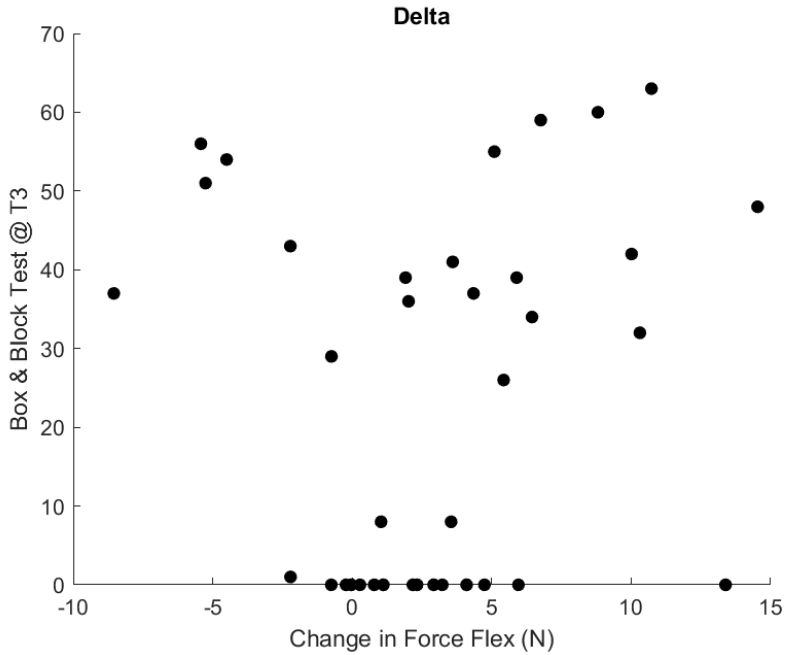
60
70
0
5
10
15
20
25

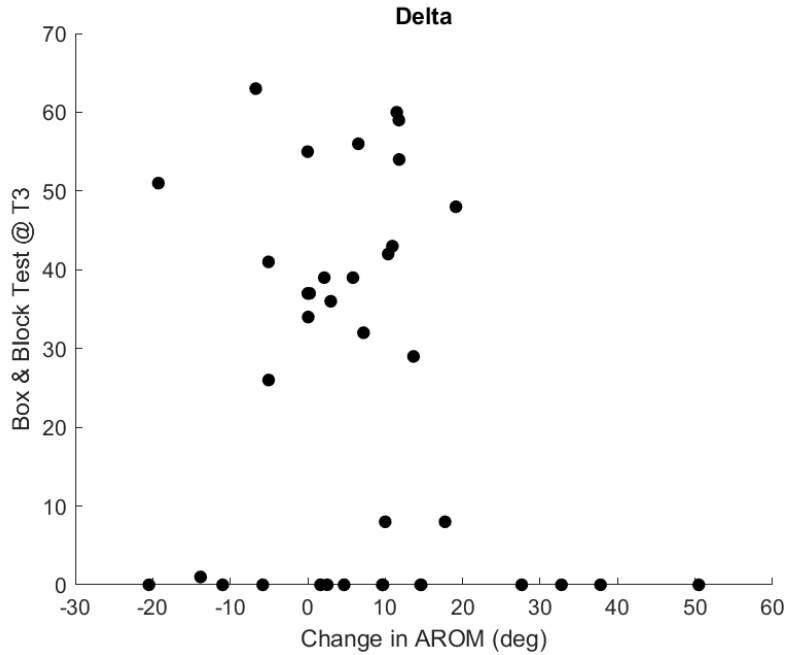
Isn’t motor function equally important?



Rho = 0.618
P-val = 4.547e-05



Rho = 0.147
P-val = 0.384



Rho = -0.143
P-val = 0.399

Delta FMA also not correlated