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Online data supplement

METHOD

Participant dropouts and exclusions

Of the baseline participants, three pre-HD, foursymp-HD and six controls did not return at 18 and 30 months. A further three pre-HD, four symp-HD and three controls did not take part at 30 months. One pre-HD participant did not contribute image data at 30 months due to pregnancy. Another pre-HD participant did not contribute T_1 data at 30 months due to claustrophobia. One control did not take part of the study at 18 months but returned at 30 months. In addition, a number of scans were excluded due to artefacts. Exclusions comprised T_1 scans from two pre-HD (magnetic susceptibility, RF noise), one symp-HD (movement) and two controls (movement) at 18 months. DWI scans excluded comprised one pre-HD and one symp-HD at baseline (acquisition fault); three pre-HD (magnetic susceptibility, RF noise), two symp-HD (RF noise and movement) and one control (RF noise) at 18 months; and two pre-HD (RF noise and movement) and two symp-HD (RF and movement) at 30 months. See Supplementary Table 1 for participant numbers at each time point included in analyses. See Supplementary Table 2 for reasons for withdrawal. See also Supplementary Table 3 for medication regime of participants.

Description of neurocognitive tasks

Speeded tapping:In each of the five trials participants tapped a mouse button repeatedly as fast as possible for 10 secondswith the index finger of the non-dominant hand.Intertap interval, ITI, was recorded.

Paced tapping: Trials began with the repeated presentation of a tone at a constant rate; when participants felt that they have a sense of the timing, they began to tap at the same rate as the tone. The tone continued for eleven more taps, but was then discontinued.Participants were asked to continue tapping, without the tone, at the same rate until the end of the trial.There were two blocks with five trials each, one using a tone at a slow rate (550ms) and the other one a tone at a faster rate (333ms). ITI was recorded and a measure of precision (the inverse of the standard deviation of the difference between the target tapping interval (TTP) and ITI, multiplied by 1000) was calculated.

Symbol Digit Modalities Test (SDMT): Participantswere presented with a page containing a key at the top that paired a series of nine symbols with the digits 1 through 9. They were instructed to use the digit-symbol pairings of the key to fill in a series of boxes, throughout the page, in which the symbol was displayed by the digit was absent.The outcome variable was number correct in 90 seconds.

Stroop word test: This test comprises a list of words (“red,” “green,”“blue”) to be read as quickly as possible by the participant. It is one of three parts of the Stroop Colour Word Interference Test, but only the word reading condition is included in the study. This is a timed paper and pencil test. The examiner uses a stopwatch to time the test. The participant reads words from a pre-printed stimulus card while the examiner records responses on a pre-printed record form. No. correct in 45 seconds was recorded.

NBACK: We used a modified version of the Callicott N-BACK paradigm (1), consisting of three conditions (0-BACK, 1-BACK and 2-BACK) administered in a block design with the 0-BACK interspersed between the 1-BACK and 2-BACK conditions. Stimuli in each trial consisted of an array of four circles arranged in a diamond-like orientation, with each of the four circles containing a number from 1 to 4 (each circle always contained the same number).

Participants used adiamond shaped button box to indicate the circle containing the number in the current trial (for the 0-BACK condition; no working memory required), or the circle that contained the number in the previous trial (1-BACK; low difficulty working memory condition), or the circle that contained the number two trials back (2-BACK; high difficulty working memory condition). The experiment was presented using a block design (i.e., 0-BACK, 1-BACK and 2-BACK each presented in separate blocks). The working memory conditions (1-BACK and 2-BACK) were presented in 4 blocks each interspersed with the 0-BACK baseline condition (8 blocks). The order of presentation of each condition was randomized such that some participants were presented with four blocks of 0-BACK 1-BACK 0-BACK 2-BACK and some were presented with four blocks of 0-BACK 2-BACK 0-BACK 1-BACK. Accuracy and response time (RT) were recorded.

Set-Response Shift (SRS): We used a modified version of the Loose et al. (2) verbal response shifting task. In every trial a single letter (B, K or M) and a single number (2, 5 or 9) were simultaneously presented on either side of a central fixation cross (750ms).During the baseline Letter condition, participants had to indicate with the left and right buttons of a button box, which side of the fixation cross contained the letter.During the active Alternate condition, the response set alternated between trials. Participants were thus required to indicate which side of the fixation cross contained the letter, and then the number, on each consecutive trial (i.e., repeatedly switching between response sets).We employed a blocked design, with the specific combinations of letter and number stimuli randomised between trials, blocks and conditions. Within each of two experimental sessions, participants completed four baseline blocks and four alternate blocks in sequential order (B A B A etc.). Accuracy and response time (RT) were recorded.

Description of neuropsychiatric questionnaires

Frontal Systems Behavioural Scale (FrSBe):This is a 46-item self-rating scale intended to measure behaviour associated with damage to the frontal systems of the brain. The FrSBeself-rating form yields a total score and scores for subscales measuring apathy (14 items), disinhibition (15 items), and executive dysfunction (17 items). Each item is rated on a 5-point Likert scale.

Schedule of Obsessions, Compulsions and Psychological Impulses (SCOPI):This is a 47 item self-report questionnaire designed to assess obsessive, compulsive and pathological impulses. The SCOPI yields a total score and scores for 5 subscales measuring Obsessive Checking, Obsessive Cleanliness, Compulsive Rituals, Hoarding and Pathological Impulses.

Statistical analysis of neurocognitive and neuropsychiatric measures

Longitudinal group differences in neurocognitive and neuropsychiatric data were investigated using a random-effects model with a generalized least squared estimator. The model included regressors for Group, Time Point and their interaction. Planned contrasts were used to test group differences, longitudinal change within all groups and longitudinal differences between HD groups (pre-HD and symp-HD separately) and controls (for results, see Supplementary Tables 5 and 6 and Supplementary Figures 1 and 2). Sex and age were included as covariates.

Partial correlations

Partial correlations were controlled for Disease Burden Score (DBS), (3) and age at baseline (4). DBS indicates the accumulated effect of mutant huntingtin at any age (3). Partialling out DBS helps control for effects of disease severity that are additional to a common propensity towards HD disease progression. However, correcting for DBS only would not account for changes that may be associated with age alone.

References

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4. Tabrizi SJ, Reilmann R, Roos RA, Durr A, Leavitt B, Owen G, et al. Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: analysis of 24 month observational data. Lancet Neurol. 2012; 11(1): 42-53.

Table DS1:$T_1$and diffusion weighted data per group at each time point.

	Controls	**Pre-HD**	**Symp-HD**
T_1 weighted			
Baseline	36	36	36
18 months	27	35	31
30 months	27	32	28
DWI*			
Baseline	36	35	35
18 months	28	34	30
30 months	27	31	25

*Diffusion weighted imaging

Table DS2:Reasons for withdrawal from the study.

	Health issues[1]	Relocated outside of study area	No reason[2]	Other[3]	Total
18 months					
Controls	1	-	5	1	7
Pre-HD		-	2	1	3
Symp-HD	1	-	1	2	4
Total	2	-	8	4	14
30 months					
Controls	-	1	1	1	3
Pre-HD	2	-	1	1	4
Symp-HD	1	1	1	1	4
Total	3	2	3	3	11
Grand total	5	2	11	7	25

[1.] Mostly undisclosed but reasons given included cancer and pregnancy
[2.] Two controls and one symp-HD at 18 months and one pre-HD at 30 months formally withdrew from the study without giving a reason. The remaining participants were uncontactable.
[3.] *e.g.*, passing of a relative; being too busy; and finding it physically difficult to attend testing.

Table DS3: Medication regime across groups and time points.

		Controls	Pre-HD	Symp-HD
Baseline				
Antipsychotics	Typical	-	-	6
	Atypical	-	1	3
Antidepressants	SSRI*	1	6	12
	Non SSRI	-	1	6
Benzodiazepines		-	1	1
18 months		-	-	-
Antipsychotics	Typical	-	-	6
	Atypical	-	1	4
Antidepressants	SSRI	-	5	14
	Non SSRI	1	3	3
Benzodiazepines		-	-	1
30 months				
Antipsychotics	Typical	-	-	4
	Atypical	-	2	6
Antidepressants	SSRI	2	4	12
	Non SSRI	2	3	3
Benzodiazepines		-	-	2

*SSRI, selective serotonin reuptake inhibitor

Table DS4. Longitudinal change in neuroimaging measures in controls, pre-HD and symp-HD groups

	Controls	χ^2	***P***	**Pre-HD**	χ^2	***P***	**Symp-HD**	χ^2	***P***
Volume (cm^3)									
Whole Brain	-8.03(3.44)	5.47	.019	-14.47(3.29)	19.33	<.001	-23.43(3.37)	48.34	<.001
Grey Matter	-2.08(2.28)	0.84	.36	-4.68(3.34)	1.96	.16	-14.04(2.94)	22.73	<.001
White Matter	-5.95(2.83)	4.43	.035	-10.10(2.71)	13.94	<.001	-6.52(2.77)	5.53	.019
CSF	0.24(3.17)	0.01	.94	2.89(3.04)	0.90	.34	16.21(3.16)	26.29	<.001
Caudate	0.013 (0.017)	0.58	.45	-0.067(0.017)	15.34	.0001	-0.166(0.017)	94.36	<.001
Putamen	-0.010(0.021)	0.22	.64	-0.055(0.021)	7.09	.008	-0.085(0.021)	16.25	.0001
Pallidum	-0.010(0.007)	2.03	.16	-0.005(0.005)	0.99	.32	-0.020(0.006)	10.43	.001
Thalamus	0.003(0.035)	0.01	.93	-0.042(0.028)	2.28	.13	-0.044(0.050)	0.79	.37
MD (s/mm^2) x 10^{-3}									
Caudate	-0.015(0.009)	2.52	.11	0.009(0.0129)	0.47	.49	0.008(0.020)	0.15	.70
Putamen	-0.025(0.005)	30.52	<.001	-0.014(0.0060)	5.39	.02	-0.004(0.010)	0.14	.71
Pallidum	-0.049(0.008)	38.56	<.001	-0.050(0.0057)	78.13	<.001	-0.030(0.009)	11.64	.001
Thalamus	-0.027(0.006)	24.2	<.001	-0.040(0.0055)	51.75	<.001	-0.026(0.006)	20.51	<.001
FA[†]									
Caudate	.0001(0.003)	0.00	.97	0.0002(0.004)	0.00	.96	.015(0.005)	9.06	.003
Putamen	.001(0.004)	0.07	.77	0.007(0.003)	4.58	.03	.014(0.005)	8.77	.003
Pallidum	.055(0.011)	25.16	<.001	0.040(0.011)	14.54	.0001	.038(0.011)	11.04	.001
Thalamus	.013(0.002)	29.75	<.001	0.013(0.002)	29.96	<.001	.010(0.003)	15.19	.0001

Data are adjusted mean changes across three testing sessions (s.e.). CSF, cerebrospinal fluid; MD, mean diffusivity; FA, fractional anisotropy.

[†] Arbitrary units.

Table DS5: Significant Group, Time and interaction effects on neurocognitive measures between 18 and 30 months. Planned contrasts.

	Group		Time			Group x Time Interaction	
	Pre-HD vs Controls	Symp-HD vs Controls	Controls	Pre-HD	Symp-HD	Pre-HD vs Controls over Time	Symp-HD vs Controls over Time
SDMT - Accuracy (No. correct)	.01	<.001	.01	.76	.92	.06	.13
Stroop (Reading)- Accuracy (No. correct)	1.0	<.001	.01	.12	.80	.86	.09
Speeded tapping - ITI (ms)	.15	<.001	.53	.93	.55	1.0	.77
Slow paced tapping (550 ms) – Precision[†]	.02	<.001	.19	.73	.24	.36	.96
Fast paced tapping (333 ms) – Precision	.02	<.001	.79	.59	.80	1.0	1.0
0-BACK - Accuracy (%correct)	.69	.003	.84	.08	.12	.20	.24
1-BACK - Accuracy (%correct)	.14	.01	.21	.09	.93	1.0	1.0
2-BACK - Accuracy (%correct)	.21	.06	.96	.41	.41	1.0	1.0
0-BACK - RT (ms)	.01	<.001	.43	.11	.06	.80	.10
1-BACK - RT (ms)	.29	.02	<.001	.01	.19	.63	.10
2-BACK - RT (ms)	.01	<.001	.01	.12	.01	.01	<.001
SRS Letters - Accuracy (%correct)	<.001	.02	.50	.41	.44	.59	.71
SRS Alternate - Accuracy (%correct)	.28	.06	<.001	.01	.32	1.0	1.0
SRS Letters - RT (ms)	.06	<.001	.85	1.0	<.001	1.0	<.001
SRS Alternate - RT (ms)	.25	<.001	.74	.30	.01	1.0	.01

Data are *P* values. SDMT, symbol digit modalities test; ITI, inter-tap interval; RT, response time; SRS, Shifting Response Set Task. Statistically significant differences at a Bonferroni-corrected threshold of $\alpha = .05$.

[†] Precision = (1/SD(TTP-ITI))*1000, that is, the inverse of the standard deviation of the difference between the target tapping interval (TTP) and ITI multiplied by 1000. TTP = 550ms in slow paced tapping and 333ms in fast paced tapping.

Table DS6: Significant Group, Time and interaction effects on psychiatric measures across 30 months. Planned comparisons.

	Group		Time			Group x Time	
	Pre-HD vs Controls	Symp-HD vs Controls	Controls	Pre-HD	Symp-HD	Pre-HD vs Controls over Time	Symp-HD vs Controls over Time
SCOPI – (Total OCD)	1.0	.21	.04	.91	.94	.23	.29
SCOPI – Obsessive checking	.40	.01	.10	.67	.53	.73	.20
SCOPI – Obsessive cleanliness	1.0	1.0	.06	.90	.42	.37	.84
SCOPI – Compulsive rituals	1.0	1.0	.03	.54	.71	.09	.13
SCOPI – Hoarding	.44	1.0	.16	.05	.42	.44	1.0
SCOPI – Pathological impulses	1.0	1.0	.02	.98	.84	.38	.79
FrSBe – Total	.17	.01	.28	.48	.16	1.0	.15
FrSBe – Apathy	.15	.02	.69	.17	.05	1.0	.18
FrSBe – Disinhibition	.45	.07	.01	.73	.34	.17	.01
FrSBe – Executive dysfunction	.06	<.001	.06	.85	.28	.47	.09

Data are *P* values. SCOPI, Schedule of Compulsions Obsessions and Pathological Impulses; FrSBe, Frontal Systems Behaviour Scale.

Statistically significant differencesat a Bonferroni-corrected threshold of $\alpha = .05$.

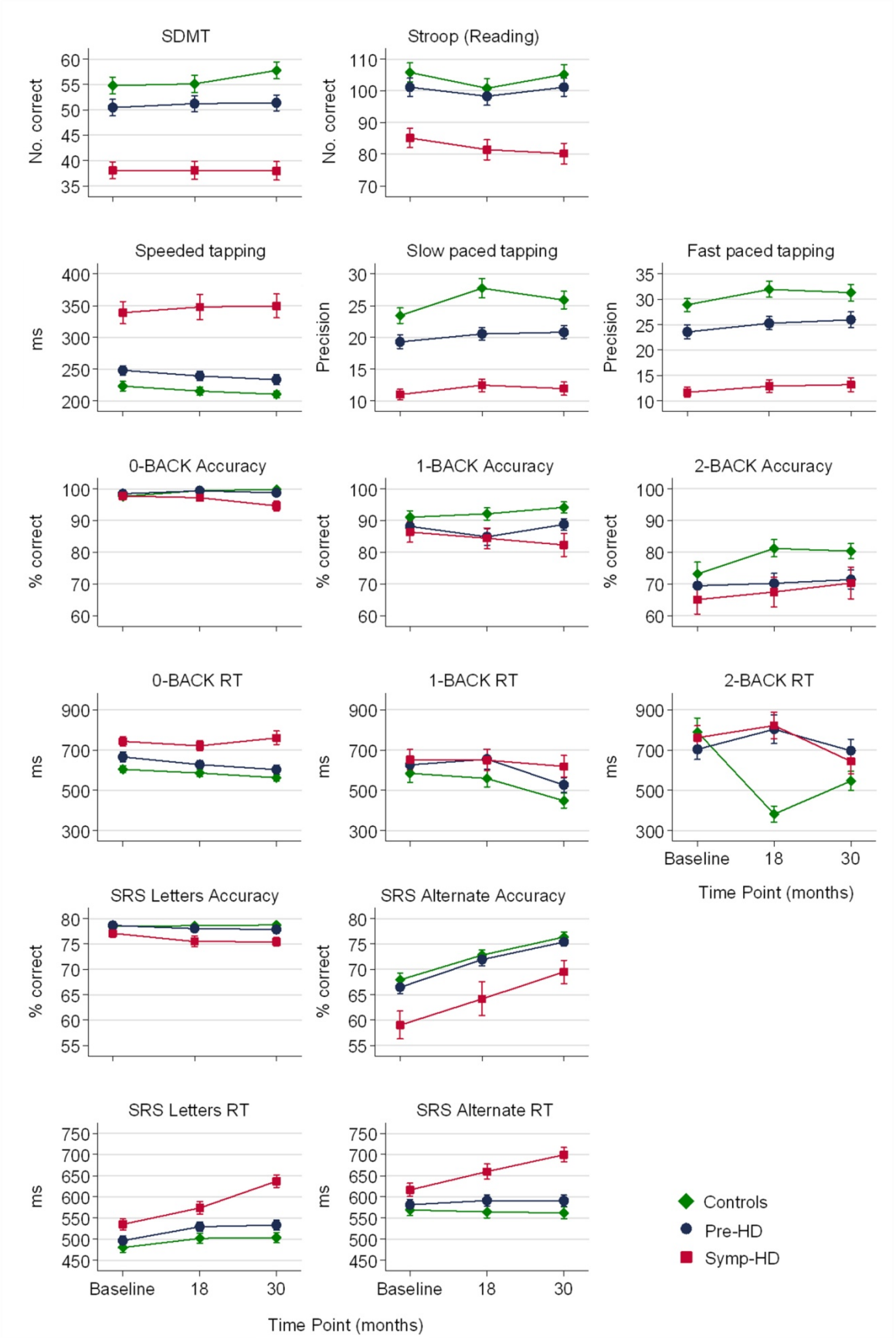

Fig. DS1 Adjusted mean (s.e.) neurocognitive measures over three testing sessions.

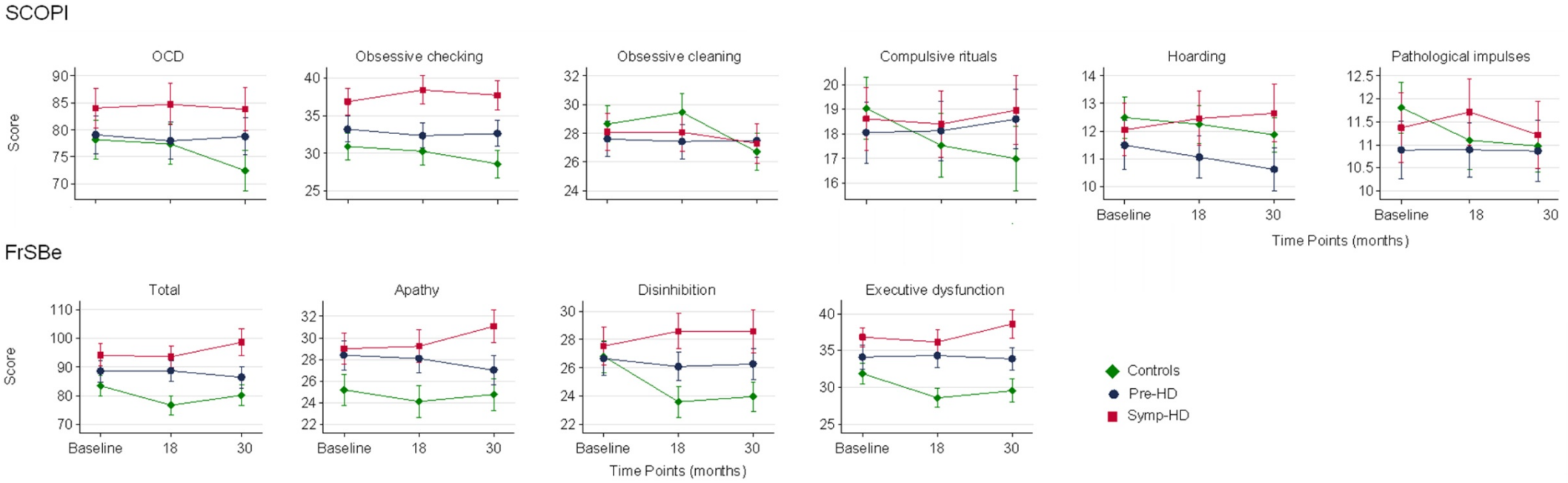

Fig. DS2 Adjusted mean (s.e.) neuropsychiatric measures over three testing sessions.