Down Syndrome Research

An agenda

Supported by funding from:

•Down Syndrome Research and Treatment Foundation
•Sie Foundation
•National Down Syndrome Foundation
•LeJeune Foundation
•Arizona Alzheimer’s Research Consortium
•Research Down Syndrome

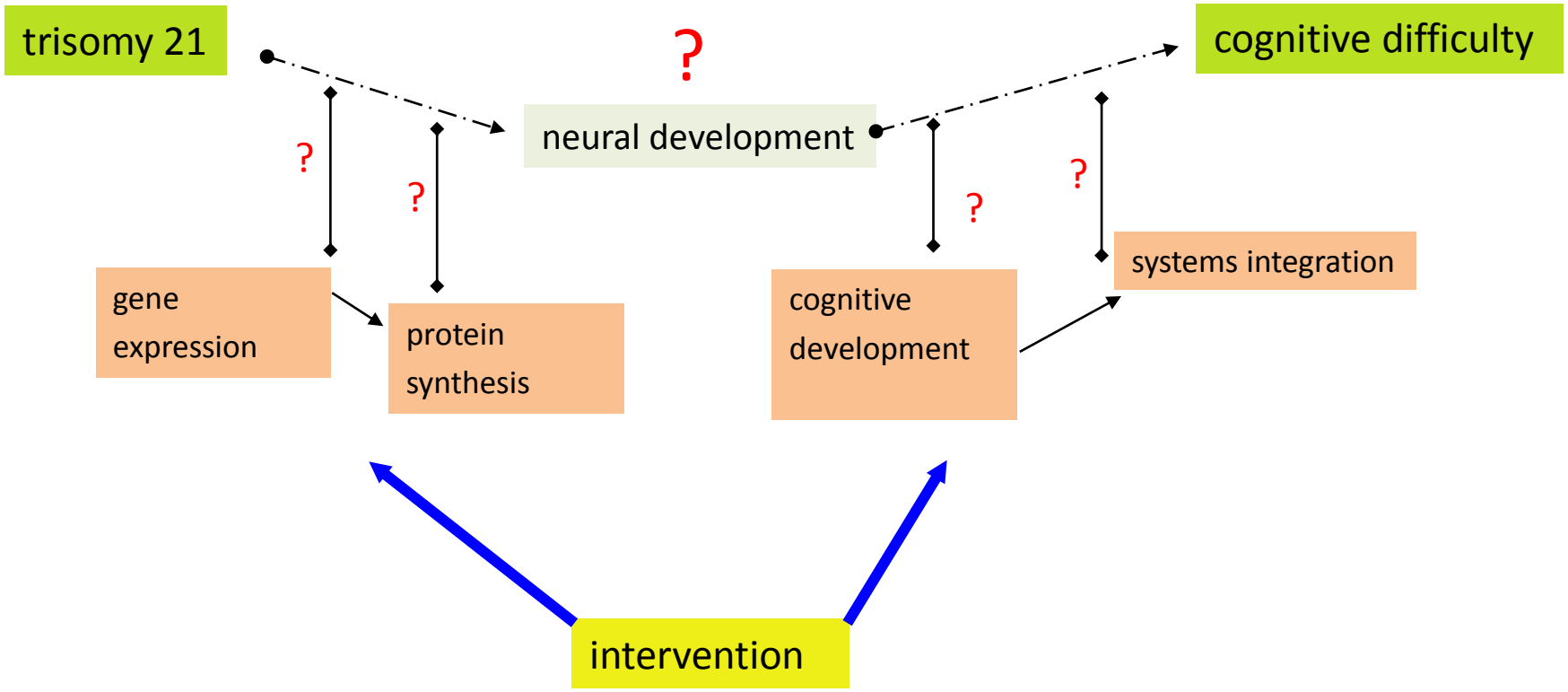
Goal

- how does a known chromosomal abnormality (trisomy 21) cause the cognitive impairments characteristic of Down syndrome.

?

trisomy 21 → cognitive difficulty

Levels of Analysis



Down Syndrome

- 1 in 800 live births; extra chromosome 21
- Moderate to severe cognitive difficulty
- Much improved prognosis since 1970s, when early stimulation programs began and institutionalization ceased
- Significant risk of Alzheimer's disease
- Intense search for cause of retardation, the sources of variation, and approaches that might ameliorate cognitive impairment

Current Situation

- Know more about cognitive impairments and neural antecedents
- Animal models capture many features of DS
- Still don’t know:
  - What explains high vs. low function
  - What genetic and environmental factors modulate cognition
  - Why some develop Alzheimer’s and others do not
  - What makes for successful intervention

Brain Development in Down Syndrome

- relatively few differences at birth
- smaller brains by 6 months of age
- diminished size of cerebellum, superior temporal gyrus, frontal lobes
- decreased dendritic arborization
- delayed myelination
- diminished metabolic activity in frontal and medial temporal lobes

MRI Morphometric Analysis of Down Syndrome Adults

Structure	Controls	Down Syndrome
Cerebrum	1101.26 + 144.49	784.01 + 20.46
prefrontal cortex	40.27 + 9.03	30.17 + 3.78
Ant. cingulate gyrus	2.68 + 0.74	0.72 + 0.33
Inf. Parietal lobe	8.95 + 1.90	6.49 + 1.24
precentral gyrus	5.30 + 0.73	4.80 + 0.62
Inf. Temporal lobe	11.32 + 1.85	9.11 + 0.90
Postcentral gyrus	8.68 + 1.70	7.33 + 0.50
Hippocampus	5.80 + 0.74	4.28 + 0.35
Caudate	7.39 + 1.18	6.28 + 0.80
Cerebellum	119.90 + 13.10	84.37 + 5.07
Parahippo. Gyrus	5.98 + 1.0	6.96 + 0.99

(from Raz, Torres, Briggs, Spencer, Thornton, Loken, Gunning, McQuain, Driesen & Acker, Neurology, 1995)

Corrected for differences in body size

Neurology of DS: Importance of Delayed Maturation

Late maturing brain structures

- **cerebellum**, **hippocampus** and **prefrontal cortex**

and components

- **inhibitory neurons**

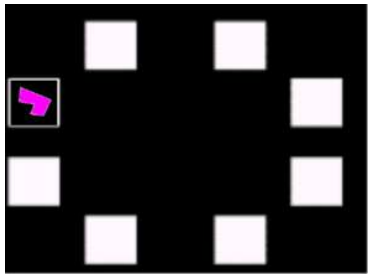
seem most at risk in Down syndrome

Hypotheses

- Prefrontal dysfunction
- Hippocampal dysfunction
- Cerebellar dysfunction
- Generalized inhibitory dysfunction

How to Test Hypothesis

Develop a test battery specific to the presumed “at-risk” structures



Battery development for the neuropsychological phenotype

Developing a Standardized Test Battery

- requires stratification of data ("high" vs. "low" on a task), therefore the best tasks will be:
  - Normally distributed or categorical
  - Have minimal floor effects
  - Minimize participant loss to gather the most representative picture
- Tasks should show consistent evidence for deficits in comparison to controls

CHALLENGE	SOLUTION
Floor effects	Use tests with graded difficulty
Language problems	Use nonverbal tasks
Behavior problems	Interview caregivers
Sensitivity	Use measures with normal distribution and continuous values. Applicable across various ages.
Flexbibility of Use	Use tests adaptable across cultures and contexts
Reproducibility	Use validated tests; collect test-retest data

Research Design

Sample

- **Down Syndrome Group:** *n* = 74, 7-38 years, IQ = 40-70.
- **Mental Age (MA) Comparison Group**: *n* = 36, ages 3-6 years.

Data Sources

- parent report of background factors, behavior and development and neuropsychological testing

4 sites

- Data collected at 4 sites:
  - Arizona, Atlanta, Baltimore and Oregon

What Didn’t Work

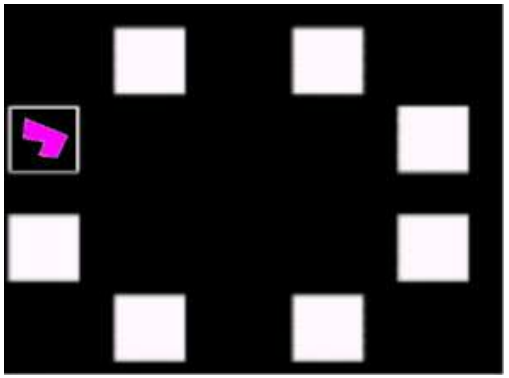
Eliminated measures:

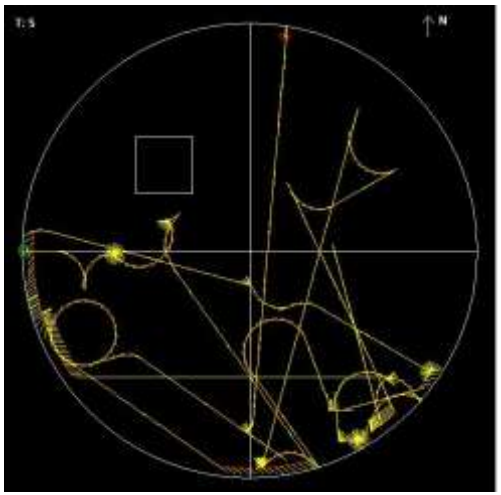
- CANTAB Spatial Recognition Memory
- Wisconsin Card Sorting Task (WCST)
- Auditory Time Estimation

Main reason: floor effects

HIPPOCAMPAL TASKS

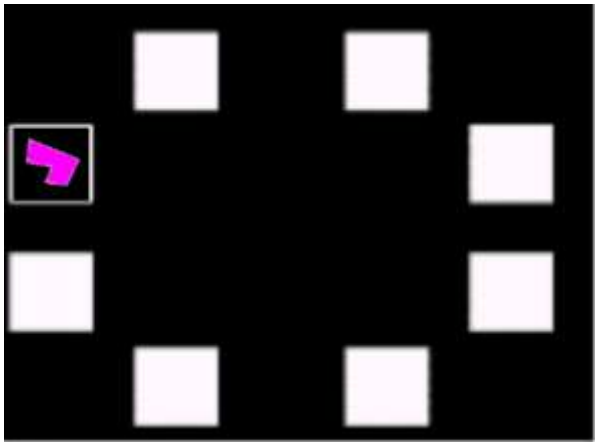
- CANTAB Paired Associates Learning
- Virtual Morris Water Maze





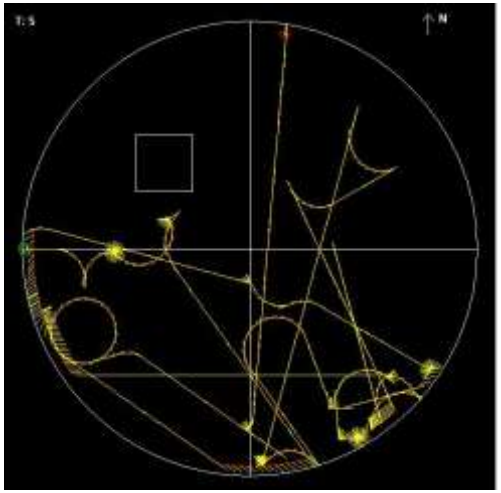
CANTAB Paired Associates Learning (PAL)

- learning associations between abstract stimuli and spatial location
- impaired in two previous studies of DS (Pennington et al., 2003; Visu-Petra, 2007)
- similar measures correlated with hippocampal volume in adults with DS (Krususki et al. 2002)
- differentiates between patients with AD and controls without dementia with 98% accuracy
- heritable in twin studies (h >.50)
- high reliability in typical populations (r= .86 for trials to success)



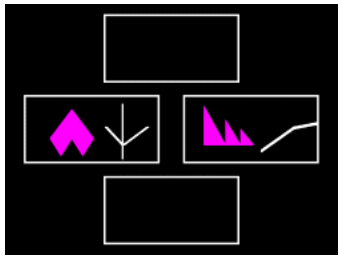
Virtual Morris Water Maze

- learning the location of a hidden target over trials
- analog measure to mouse model deficit
- impaired in Pennington et al. (2003)
  and in hippocampal patients



Virtual Morris Water Maze

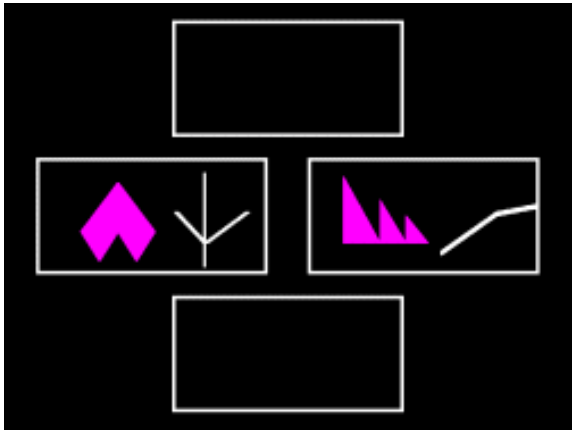
PREFRONTAL TASKS



- CANTAB Intra-dimensional/Extra-dimensional set-shifting
- Frogs/Cats test of inhibitory control and working memory
- BRIEF assessment of executive function parent report

CANTAB Intra-dimensional/Extra-dimensional set-shifting (ID/ED)

- learning and shifting between arbitrary rules
- impaired in autism and frontal lesions
- deficits reduced with dopaminergic medicine in Parkinson's
- temporal lobe and AD patients unaffected
- included in NIH study of brain development
- acceptable reliability (r = .70 for errors)



Frogs/Cats test of Inhibitory Control and WM

- inhibition of a previous rule and juggling two rules
- combined phase activates the PFC in fMRI studies with children (Davidson et al., 2006)
- related to dopamine gene (*COMT*) (Diamond et al., 2004)

Cats - Congruent response

Push Left

Push Right

Frogs – Incongruent response

Push Right

Push Left

Combined Condition

BRIEF Inventory of Executive Function

- widely used parent report measure of everyday executive skills across populations
- included in NIH study of brain development

CEREBELLAR TASKS

CANTAB Simple Reaction Time

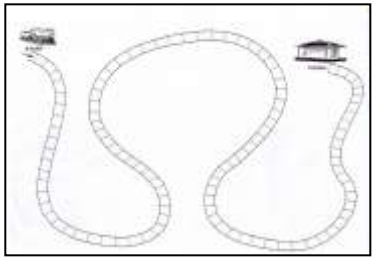
- simple button press to a visual stimulus
- slowing of motor response time typical with cerebellar dysfunction
- several studies have reported slowed reaction times in DS (Anson, 1989; Brian & Hayes, 1989)

NEPSY Sequential Finger Tapping

- touching finger to thumb in sequence (1-4 fingers)
- activates the cerebellum in fMRI studies (Desmond et al., 1997)

NEPSY Visuomotor Precision

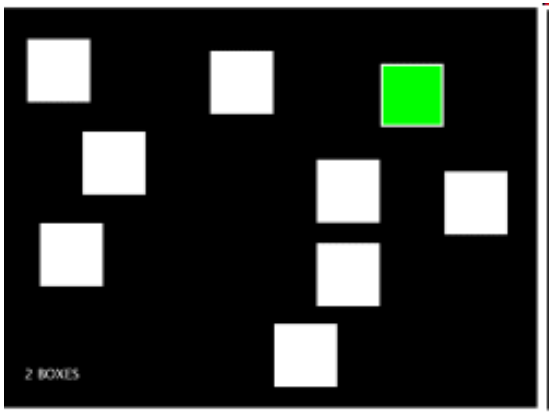
- visuo-motor tracking utilizing coordinated hand-eye movements activates the cerebellum (Miall et al., 2000)



Control task: CANTAB Spatial Span

- immediate memory for a sequence of locations
- control task- no impairment in previous studies

- ***<u>no</u> impairment in our sample (p>.55)***



Measure	DS *Mean (SD)* (N=55)	MA Control *Mean (SD)* (N=36)	*t/z*	*p*	Effect Sizes *d*
Background and Benchmark					
KBIT-II verbal score	26.40 (10.33)	27.39 (5.49)	-0.59	0.60	--
KBIT-II non-verbal score	13.66 (4.51)	13.97 (3.44)	-0.36	0.72	--
CANTAB Spatial Span span	2.58 (1.26)	2.88 (1.07)	-1.17	0.25	--
Hippocampal					
CANTAB first trials completed	5.57 (3.40)	3.70 (2.55)	2.77	0.007	0.62
Computer generated arena % time in the target quadrant	26.73 (19.83)	20.69 (21.19)	1.25	0.21	--
Prefrontal					
CANTAB ID/ED errors per stage*	5.02 (2.91)	3.86 (1.44)	-2.60	0.009	0.51
Modified Dots Task inhib. control phase percent correct	67.31 (32.46)	75.62 (21.30)	-1.37	0.18	0.30
Modified Dots Task combined phase percent correct	57.28 (18.43)	66.55 (22.26)	-1.97	0.05	0.45
Cerebellar					
CANTAB Simple RT median corr. latency (ms)	678.93 (314.46)	595.88 (142.69)	1.64	0.11	0.34
NEPSY Visuomotor Precision total score	15.08 (5.34)	14.57 (4.69)	0.41	0.69	--
NEPSY Finger tapping mean latency (all trials) (s)	44.97 (20.36)	33.92 (12.64)	2.62	0.01	0.65

Correlations with Parent Report

- shows specificity in the scales
  - BRIEF scores related to:
    - ID/ED errors (r =.40, p=.01)
    - number correct on frogs and cats inhibitory control (r =-.43, p =.01)
    - No correlations with hippocampal measures
- neuropsychological measures related to adaptive behavior
  - SIBR scale related to:
    - frogs and cats inhibitory control (r =-.44, p =.03)

Distribution data for each battery measure

Measure	n*	% not completed	% floor[a]	mean	SD	range	skewness	kurtosis
Background and Benchmark								
SIB-R adaptive behavior standard score	70	5.4	10.0	36.50	25.28	2-89	0.18	-0.89
KBIT-II verbal total score	70	5.4	0.0	22.53	11.95	2-59	0.66	0.73
KBIT-II non-verbal total score	70	5.4	5.7	11.89	5.64	0-27	-0.23	0.24
CANTAB Spatial Span span	66	10.8	33.3	2.30	1.27	1-6	0.67	-0.08
Hippocampal								
CANTAB PAL first trials correct	71	4.1	14.1	7.42	6.01	0-22	0.42	-0.80
Computer generated arena % time in the target quadrant	63	14.9	22.2	24.05	20.22	0-77	0.54	-0.26
Prefrontal								
CANTAB ID/ED errors per stage (ln transformed)	67	9.5	14.9	5.45	3.99	1.33-26	-0.85	0.27
Modified Dots Task inhib. control phase percent correct	65	8.5	29.2	63.59	31.85	0-100	-0.41	-.92
Modified Dots Task combined phase percent correct	65	8.5	41.5	54.13	18.30	15-100	1.08	1.15
Cerebellar								
CANTAB Simple RT median corr. latency (ms)	66	10.8	25.8	735.26	321.39	275-1656	0.79	0.10
NEPSY Visuomotor Precision total score	48	9.4	0.0	59.31	45.24	24-336	-0.48	-1.09
NEPSY Finger tapping mean latency (all trials) (s)	43	18.9	7.0	44.11	20.77	19.37-82.50	0.62	-1.17

Conclusions

- **measures show sensitivity to detect deficits in hippocampal, prefrontal and cerebellar function**

- **evidence for measure validity**
  - **specificity in scales from factor analyses**
  - **concurrent validity established through correlations with parent report**

- **measures show minimal participant loss and sufficient variability**

Current Projects

- Assess sleep quality and relation to cognitive function
  - About 90% of DS children have impaired sleep quality
- Relate COMT allele status to prefrontal function
  - “bad” alleles correlated with poor PFC function
- Assess impact of memory training
  - Just starting
- Test-Retest reliability over 3-6 months

Going Forward

This battery can be used to:

- evaluate treatments and early stimulation regimes
- develop better animal models
- accurate characterization of each individual with Down syndrome, making it possible to optimize every child's outcome

Results: Relative Specificity in factors

Rotated Component Matrix[a]

	Component		
	1	2	3
PAL Mean errors to success	.320	.180	-.777
Dwell time at target	.229	.021	.823
Mean Simple RT	.326	.901	.013
Rate change in tapping	.131	-.624	.411
Frogs/CATS	.844	-.043	.096
Shifting on DCCS	-.681	.635	.090
IDED errors	.808	.245	-.055

Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization.

a. Rotation converged in 5 iterations.

Domain/test	Description	Primary ability assessed	Score for analysis	Test-retest *r*	Links to brain function
Benchmark					
KBIT-II Verbal Subscale (Kaufmann, 2004)	Points to pictures based on the word or phrase, answers riddles	Verbal comprehension, production	total subscale raw	.88	--
KBIT-II Nonverbal Subscale	Semantic or visuo-spatial pattern completion	Problem solving	total subscale raw	.76	--
Scales of Independent Behavior- Revised (Bruininks, 1997)	Parent-report of everyday skills	Adaptive behavior	standard score	.98	--
CANTAB Spatial Span	Touching of boxes in order changing color on the screen, similar to CORSI span	Immediate memory for spatial-temporal sequences	span	.64 (Lowe and Rabbitt, 1998)	--
Prefrontal					
Modified Dots task	Presses a button below a cat, shifts to a new rule (pressing across the screen) for a frog, shifts between rules	Inhibitory control, working memory	percent correct trials	*NA*	activates prefrontal cortex in children in fMRI studies (Davidson, 2006).
CANTAB IED	Forced-choice discrimination task with change in relevant dimension	Set-shifting	errors per stage (ln transformed)	.70 (Lowe and Rabbitt, 1998)	Impaired in populations with frontal deficits (e.g., autism, Ozonoff, 2004). Deficits are ameliorated by dopaminergic medication (Strauss, Sherman & Spreen, 2006).

Hippocampal

CANTAB Paired Associates	Recall for hidden abstract patterns and associated locations	Spatial associative memory	errors to success, number trials completed on first view	.87 (average trials to success, Lowe and Rabbitt, 1998)	Differentiates between patients with AD and controls with 98% accuracy 18 months prior to a formal diagnosis (Swainson, 2001).
Virtual computer-generated arena	Navigation of a virtual arena (via joystick) to find a fixed hidden target	Spatial memory	percent time searching target quadrant	*NA*	Patients with hippocampal damage impaired (Skelton, 2000).

Cerebellar

NEPSY Fingertip Tapping (modified) (Korkman, Kirk & Kemp, 1998)	Sequences generated by tapping fingers (1,2,3,4) to the thumb in succession	Motor sequencing	latency across trials	.71	Finger sequencing activates cerebellum (Desmond, 1997).
NEPSY Visuomotor Precision (ages 3-4) (Korkman, Kirk & Kemp, 1998)	Follows two tracks with a pen	Visuo-motor tracking, hand-eye coordination	Total score generated from completion time and errors	.81	Visuo-motor tracking utilizing coordinated hand-eye movements activates cerebellum (Miall, 2000).
CANTAB Simple Reaction Time (SRT)	Participants press a button in response to a box presented on a screen	Motor response time and attention	median correct latency	*NA*	Simple motor response and attention tasks activate the cerebellum in fMRI (Allen et al., 1997).

Percent of individuals with floor performance for each test by age group.

Test	Age Group (years) 7-11 *(N = 30)	12-17 (N = 25)	18-38 (N = 19)	χ^2	*p*
Background and Benchmark					
SIB-R adaptive behavior standard score	14.8	8.3	5.3	1.24	0.54
KBIT-II standard score	46.4	60.9	52.6	1.06	0.59
KBIT-II verbal score	0.0	0.0	0.0	--	--
KBIT-II non-verbal score	10.7	4.3	0.0	2.53	0.28
CANTAB Spatial Span span	58.3	34.8	15.8	8.30	0.02
Hippocampal					
CANTAB PAL first trials correct	20.7	12.3	5.3	2.29	0.32
Computer generated arena % time in the target quadrant	50.0	14.3	11.1	9.24	0.01
Prefrontal					
CANTAB ID/ED errors per stage	32.0	4.3	5.3	9.16	0.01
Modified Dots Task inhib. control phase percent correct	48.0	23.8	10.5	7.79	0.02
Modified Dots Task combined phase percent correct	60.0	38.1	21.1	6.90	0.03
Cerebellar					
CANTAB Simple RT median corr. latency	52.0	13.0	5.6	14.79	<0.001
NEPSY Visuomotor Precision total score	0.0	0.0	0.0	--	--
NEPSY Finger tapping latency (all trials)	7.1	6.7	7.1	0.003	0.99