CHAPTER 5

Repeated administration of a neurocognitive test battery in healthy children

Submitted for publication

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Abstract

BACKGROUND This study was performed to assess the suitability of a selection of tasks from a neurocognitive test battery (Neurocart) in healthy children aged 8-12 years. Utilizing the Neurocart in the pediatric age group would be particularly attractive, as it provides a non-invasive method of gathering an extensive amount of data in different settings, including interventional research.

METHODS We designed this study to establish whether it would be feasible to repeatedly complete the neurocognitive tasks and to establish inter- and intra-individual variance of task results upon test repetition. We also assessed the influence of age on the obtained measurements. A short questionnaire was completed upon study completion to evaluate how children had experienced the study procedures.

RESULTS The 15 participating children completed 3 consecutive runs of tasks (Stroop task, body sway, adaptive tracking, smooth pursuit eye movements, saccadic eye movements, finger tapping). A significant learning effect was observed in the Stroop task, smooth pursuit eye movement task, saccadic eye movement tasks and adaptive tracking task. By linear regression analysis, significant effects of age on the Stroop task and body sway task were demonstrated. Judging by the questionnaire results, performing these tasks does not seem to be burdensome for participating children.

CONCLUSION The selection of neurocognitive tasks used in this study seems suitable for interventional research in individuals within the age range of 8-12 years.

Introduction

Neurocognitive tasks can form a useful tool in the research area of clinical pharmacology. Task results can be used to characterize certain study populations, or, more interestingly, can serve as a tool to measure or quantify the (side-) effect of interventions such as the administration of neurotropic drugs. The Neurocart is a test battery consisting of a set of well-known neurocognitive tasks, which has been used extensively in our centre, and which is strongly founded in the literature (1, 2).

Utilizing the Neurocart in the pediatric age group would be particularly attractive, as it provides a non-invasive method of gathering an extensive amount of data in different settings, including (drug) trials. Minimal risk and burden are a requirement for non-therapeutic drug trials in this age group (International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH Harmonised tripartite guideline E11-Clinical investigation of medicinal products in the pediatric population, 2000). The need for adequately validated and non-invasive biomarkers of drug effects has increased over the past years, with a legal framework in place forcing industry to evaluate new drugs in all age groups (3).

When designing trials to be performed in the pediatric age group, the investigator is faced by some unique challenges. As mentioned earlier, there is a much lower threshold for risk and burden. Secondly, if active participation from the part of a participating child is required, as for instance with neurocognitive tasks, the investigator will have to establish whether children will be able to complete the required tasks without losing their attention. Finally, results may be influenced by developmental differences across age groups. For example, eye movement tasks were shown to be influenced by developmental changes from childhood into adolescence (4, 5).

As a preparatory effort towards utilizing our Neurocart test battery in clinical studies in the pediatric population, we designed a pilot study in

healthy children to establish whether it would be feasible to (repeatedly) complete a set of neurocognitive tasks and to establish inter- and intra-individual variance of task results upon test repetition. We wanted to assess how children experienced participation by means of a short structured questionnaire to confirm our view that these procedures fall within the ethical requirement of 'minimal risk and burden'. Finally, we aimed to assess a possible influence of age on the obtained measurements.

Materials and methods

STUDY DESIGN

This was an observational study in healthy children aged 8-12 years. Exclusion criteria were: any known psychiatric diagnosis (e.g. autism, oppositional defiant disorder, ADHD); dyslexia; learning disability; significant behavioural problems; use of any medication and preterm birth. The Medical Ethics Committee of the Leiden University Medical Centre approved the study protocol. In compliance with the Declaration of Helsinki, written informed consent was obtained from the parents or legal guardians of the participating children.

NEUROCOGNITIVE TASKS

Two single-trial computerized versions of the classic *colour-word Stroop tasks* (6) were presented to the test subjects. In the first trial, 20 coloured items were presented at random. The subjects were asked to respond as fast and as accurate as possible by pressing the keys 1, 2 or 3 on the numerical pad with the index finger, middle finger and ring finger of the dominant hand, corresponding with the correct answer. In the second trial, which appeared directly after the first trial, 20 colour and word pairs were presented randomly to the subject, forming either congruent or incongruent matches. The subjects were again asked to respond as fast as possible by pressing the keys 1, 2 or 3 on the numerical pad, corresponding with the correct answer. In both trials, reaction times and the number of correct responses were recorded.

The *adaptive tracking test* is a pursuit-tracking task. A circle of known dimensions moves randomly about a screen. The test subject must try to keep a dot inside the moving circle by operating a joystick. If this effort is successful, the speed of the moving circle increases. Conversely, the velocity is reduced if the test subject cannot maintain the dot inside the circle. In contrast to non-adaptive tracking methods, this leads to a constant and individually adapted challenge throughout the procedure. Performance is scored after a fixed period. The adaptive tracking test was performed as originally described by Borland and Nicholson (7, 8), using customised equipment and software (Hobbs, 2004, Hertfordshire, UK). The average performance and the standard deviation of scores over a 3.5-minute period were used for analysis. This 3.5-minute period included a run-in time of 0.5 minute; in this run-in time the data were not recorded.

The use of a computer for measurement of *saccadic eye movements* was originally described by Baloh (9). In this study we used the nystagmo stimulator for stimulus display from Nihon Kohden (Nihon Kohden Corporation, Tokyo, Japan), the program for signal collection and the AD-converter from Cambridge Electronic Design (CED Ltd., Cambridge, UK), the amplification by Grass (Grass-Telefactor, An Astro-Med, Inc. Product Group, Braintree, USA) and the sampling and analysis scripts were developed at the CHDR (Leiden, the Netherlands). Disposable electrodes were applied on the forehead and beside the lateral canthi of both eyes of the subject for registration of the electro-oculographic signals. Head movements were minimised with the aid of a head support placed opposite the target. The target consists of an array of light emitting diodes on a bar, fixed at 50 cm in front of the head support. Saccadic eye movements were recorded for stimulus amplitudes of approximately 15 degrees to either side. Fifteen saccades were recorded with interstimulus intervals varying randomly between 3 and 6 seconds. Average values of latency (reaction time), saccadic peak velocity of all *correct*

saccades and inaccuracy of all saccades were used as parameters. Saccadic inaccuracy was calculated as the absolute value of the difference between the stimulus angle and the corresponding saccade, expressed as a percentage of the stimulus angle.

The same system as used for saccadic eye movements was also used for measurement of *smooth pursuit*. For smooth pursuit eye movements, the target moves sinusoidally at frequencies ranging from 0.3 to 1.1 Hz, by steps of 0.1 Hz. The amplitude of target displacement corresponds to 22.5 degrees eyeball rotation to both sides. Four cycles were recorded for each stimulus frequency. The time in which the eyes are in smooth pursuit of the target were calculated for each frequency and expressed as a percentage of stimulus duration. The average percentage of smooth pursuit for all stimulus frequencies was used as parameter.

Finger tapping has been adapted from the Halstead Reitan Test Battery (10), and evaluates motor activation and fluency. In this test, speed of finger tapping was measured for the index finger of the dominant hand; a session contains five 10-second trials. Feedback on performance was given by a counter in the centre of the screen, while the amount of taps of each 10-second trial was shown on the screen in between the trials. The space bar was used as tapping device. The children were instructed to tap as quickly as possible with the index finger and to rest the wrist on the table. The mean tapping rate and the standard deviations for the dominant hand were used for statistical analysis.

The *body sway* meter allows measurement of body movements in a single plane, providing a measure of postural stability. Body sway is measured with an apparatus similar to the Wright ataxiameter (11). With a string attached to the waist, all body movements in the sagittal (forward/backward) plane over a period of 2 minutes are integrated and expressed as mm sway on a digital display. Children were instructed to keep the eyes closed to eliminate the contribution of vision to postural control. Before starting a measurement, children were asked to stand still and comfortable, with their feet approximately 10 cm part and their hands in a relaxed position alongside the body.

STUDY DAYS

Participants were asked to come to the study centre accompanied by their parents for a single occasion, where they consecutively performed three runs of the aforementioned neurocognitive tasks. After completing the three runs of testing, children were asked to complete a structured questionnaire on how they experienced participation, in order to evaluate the research burden.

STATISTICS

To estimate the variances an analysis of variance was done. Body Sway data were log-transformed to meet the requirements for the analysis of variance parameters.

The parameters were analysed with a mixed model analysis of variance with time as fixed factor, subject as random factor and a variance components covariance structure. The covariance parameter estimate for subject is the inter-subject variance, the covariance parameter estimate for the residual the intra-subject variance. To eliminate the age effect from the inter-subject variability, the analysis was repeated with the same model and age as covariate. Coefficients of variation were calculated. Run-to-run contrasts were calculated within the model with estimated means of the difference and 95% confidence intervals. To establish the effect of age on the results of the different measurements, a linear regression analysis was performed using averaged measurements for each test parameter per subject. R square values were calculated, and the null hypothesis of the slope being equal to zero was tested. All statistical calculations were performed using SAS version 9.1.3 (SAS Institute, Inc, Cary, NC, USA).

Results

The study was completed by 15 children (8 males, 7 females; age 10.64 ± 1.31 years).

Means of all measurements (i.e. all measurements for each task pooled), with calculated inter- and intra-individual coefficients of variation are presented in table 1. Estimated means of measurements per run, including run-to-run comparisons are presented in table 2. Run-to-run increase in performance was statistically significant in the Stroop task, Smooth pursuit eye movement, Saccadic eye movements and adaptive tracking tasks.

The linear regression analysis results are presented in table 3. Clear age dependent changes in test results are observed in several neurocognitive tasks, as represented in figures 1a-c. Generally, task performance improves with increasing age. The age dependent change is statistically significant for the Stroop task reaction times and for the body sway task. However, a considerable residual error remains, as indicated by relatively low R-square values.

Results of the post-study questionnaire are presented in table 4. Children tended to rate participation rather positively, with 53.3% of children enjoying participation 'quite much' and 46.6 % of children 'very much'. Two-thirds would participate again when asked. Some tests were clearly appreciated more (tapping task) than others (adaptive tracking).

Discussion

In this study, a battery of neurocognitive tasks (Neurocart) was administered repeatedly in healthy children aged 8-12. For several tasks, repeated administration was shown to increase task performance. Age dependent changes in task performance were also demonstrated. Intra- and inter-individual coefficients of variation, calculated for pooled results of all 3 measurements in all 15 subjects, were relatively large. In part, this observation can be explained by the effects of repeated administration (such as learning effects, boredom, fatigue; leading to increased intra-individual variance), and the effect of age (leading to increased interindividual variance).

Age effects were not observed in any task. Eye movements in particular were strikingly constant within the age range of our study population, suggesting that the neuronal network responsible for eye movements has matured at a young age (12), or that the maturational process is slow within this age range. On the other hand, some tasks displayed clear effects of age. As an example, in our study postural stability improved significantly with increasing age, consistent with existing literature (13). The participating children in our study were all able to complete the tasks. Participation in the study was well tolerated, as reflected by the favorable responses to our post-study questionnaire. In our opinion, performing these tasks can therefore be viewed as 'minimal burden' in the context of the medical-ethical review process.

Learning effects were clearly observed in several of the administered neurocognitive tasks. Other tasks, in particular the simple motor tasks (tapping, eye movements, postural stability) did not show any learning effect). It could be speculated that tasks requiring higher cortical levels display greater learning effects than tasks addressing simple motor abilities.

The main goal of this study was to establish the feasibility of employing the Neurocart in pharmacological intervention studies with children. Judging by the responses to the questionnaire completed after participation, performing the tasks does not seem to be burdensome in this age group. Learning effects and age effects are both factors that would need to be taken into account when employing the Neurocart in interventional research. Studies employing the Neurocart in the pediatric age group should be carefully designed to avoid any confounding by the aforementioned effects. For example, learning effects might be controlled

by performing one or several 'run-in' cycles of testing,and comparison of measurements between different groups would require meticulous age-matching.

In conclusion, the selection of neurocognitive tasks used in this study seems suitable for employing in interventional research in individuals within the age range of 8-12 years. The non-invasive nature of these methods make them particularly suitable for use in pediatric age groups. In the setting of pharmacological research, this would typically entail comparison of task results after administration of active drug or placebo to demonstrate central (side)- effects of the drug studied, and/or repeated administration of tasks to estimate the duration of the observed effect.

TABLE 1 Mean of all obtained measurements (3 measurements per individual), with calculated intra- and inter-subject coefficient of variation and inter-subject coefficient of variation corrected for age.

Parameter	Mean	Intra-subject cv	Inter-subject cv	Inter-subject cv (corrected for age)
Stroop Basic, # correct	18.8	5.12	5.63	5.39
Stroop Basic, reaction time (ms)	681	13.1	19.0	17.1
Stroop Conflict, # correct	19.0	4.97	4.55	4.56
Stroop Conflict, reaction time (ms)	840	13.9	23.3	20.8
Smooth pursuit (%)	34.8	14.0	22.9	23.6
Saccadic Inaccuracy (%)	6.18	23.5	21.7	21.4
Saccadic peak velocity (degr/sec)	537	3.83	8.99	9.33
Saccadic reaction time (ms)	221	9.94	10.1	9.95
Tapping (/10 sec)	55	3.16	11.3	10.3
Tapping St. Dev.	3.84	27.9	25.1	23.6
Adaptive tracking (%)	16.4	11.0	24.3	22.6
Adaptive Tracking St. Dev.	2.78	20.2	13.0	13.4
Body Sway (mm; log-transformed)	5.88	18.0	50.3	40.8

TABLE 2 Least square means estimates for each task per run, and statistical significance of run-to-run contrasts.

Parameter		Est. mean (95% CI)	x Run 2 (p-value)	x Run 3 (p-value)
Stroop Basic, # correct	Run 1	18.7 (18.0-19.4)	0.26	0.85
	Run 2	19.1 (18.4-19.8)	-	0.35
	Run 3	18.7 (18.0-19.4)	-	-
Stroop Basic, reaction time (ms)	Run 1	731 (652-811)	0.06	0.01
	Run 2	669 (589-748)	-	0.43
	Run 3	643 (563-722)	-	-
Stroop Conflict, # correct	Run 1	18.7 (18.1-19.3)	0.70	0.06
	Run 2	18.9 (18.3-19.5)	-	0.13
	Run 3	19.4 (18.8-20.0)	-	-
Stroop Conflict, reaction time (ms)	Run 1	882 (765-999)	0.37	0.06
	Run 2	843 (726-960)	-	0.29
	Run 3	797 (680-914)	-	-
Smooth pursuit (%)	Run 1	31.5 (26.7-36.2)	<0.01	<0.01
	Run 2	36.6 (31.7-41.5)	-	0.83
	Run 3	37.0 (32.1-41.9)	-	-
Saccadic Inaccuracy (%)	Run 1	7.05 (6.08-8.02)	0.10	<0.01
	Run 2	6.09 (5.12-7.06)	-	0.24
	Run 3	5.45 (4.51-6.39)	-	-
Saccadic peak velocity (degr/sec)	Run 1	558 (530-586)	<0.01	<0.0001
	Run 2	531 (503-559)	-	0.21
	Run 3	521 (493-549)	-	-
Saccadic reaction time (ms)	Run 1	214 (199-230)	0.41	0.11
	Run 2	221 (206-237)	-	0.44
	Run 3	228 (213-243)	-	-
Tapping (/10 sec)	Run 1	55.3 (51.8-58.8)	0.28	0.45
	Run 2	54.6 (51.1-58.1)	-	0.76
	Run 3	54.8 (51.3-58.3)	-	-
Tapping St. Dev.	Run 1	3.73 (3.05-4.41)	0.77	0.31
	Run 2	3.61 (2.93-4.30)	-	0.20
	Run 3	4.14 (3.44-4.85)	-	-
Adaptive tracking (%)	Run 1	14.9 (12.6-17.2)	<0.01	<0.01
	Run 2	17.0 (14.7-19.4)	-	0.76
	Run 3	17.3 (14.9-19.6)	-	-
Adaptive Tracking St. Dev.	Run 1	2.75 (2.45-3.05)	0.93	0.66
	Run 2	2.73 (2.43-3.04)	-	0.61
	Run 3	2.84 (2.54-3.14)	-	-
Body Sway (mm; log-transformed)	Run 1	5.84 (5.56-6.12)	0.64	0.17
	Run 2	5.87 (5.59-6.15)	-	0.36
	Run 3	5.93 (5.65-6.22)	-	-

TABLE 3 Tabulated results of linear regression analysis. For each test parameter, measurement results were averaged per subject. The y-axis intercept, regression coefficient (slope of the regression line), R-square values and p-values are presented.

Parameter	y-axis Intercept	Regression coefficient	R-square	p-value (slope ≠ 0)
Stroop Basic, # correct	16.4	0.24	0.11	0.22
Stroop Basic, reaction time (ms)	1194	-50.6	0.30	0.03
Stroop Conflict, # correct	18.9	0.02	0.00	0.88
Stroop Conflict, reaction time (ms)	1660	-79.0	0.29	0.04
Smooth pursuit (%)	44.5	-0.91	0.02	0.59
Saccadic Inaccuracy (%)	9.65	-0.33	0.11	0.24
Saccadic peak velocity (degr/sec)	549	-1.20	0.00	0.91
Saccadic reaction time (ms)	273	-4.90	0.08	0.31
Tapping (/10 sec)	30.1	2.33	0.24	0.06
Tapping St. Dev.	0.06	0.35	0.21	0.08
Adaptive tracking (%)	2.26	1.33	0.19	0.10
Adaptive Tracking St. Dev.	2.52	0.02	0.01	0.75
Body Sway (mm; log-transformed)	8.4	-0.24	0.46	<0.01

TABLE 4 Results of the post-study questionnaires taken after completion of the 3 test-runs.

Question	Answer	(%)
How did you like participating in this study?	Not at all	0
	Not much	0
	Quite much	53.3
	Very much	46.7
How did you like the duration of the tests?	Much too long	0
	Long	33.3
	Not too long	60
	Short	6.7
	Much too short	0
Would you participate again?	Yes	66.7
	No	6.7
	Not sure	26.7
The electrodes on my forehead were:	Very annoying	0
	A little annoying	33.3
	Not so annoying	20
	Not at all annoying	46.7
The task I enjoyed the most was:	Stroop	13.3
	Adaptive tracking	0
	Eye pursuit tasks	33.3
	Body Sway	6.7
	Tapping	46.7
The task I disliked most was:	Stroop	0
	Adaptive tracking	83.3
	Eye pursuit tasks	3.3
	Body Sway	13.3
	Tapping	0

FIG. 1A-C Graphical representation of the linear regression analysis for Stroop reaction time (basic condition), Stroop reaction time (conflict condition) and body sway with age. The dots represent the average of 3 test runs for each subject. (for regression coefficients and R-square values, refer to table 3).

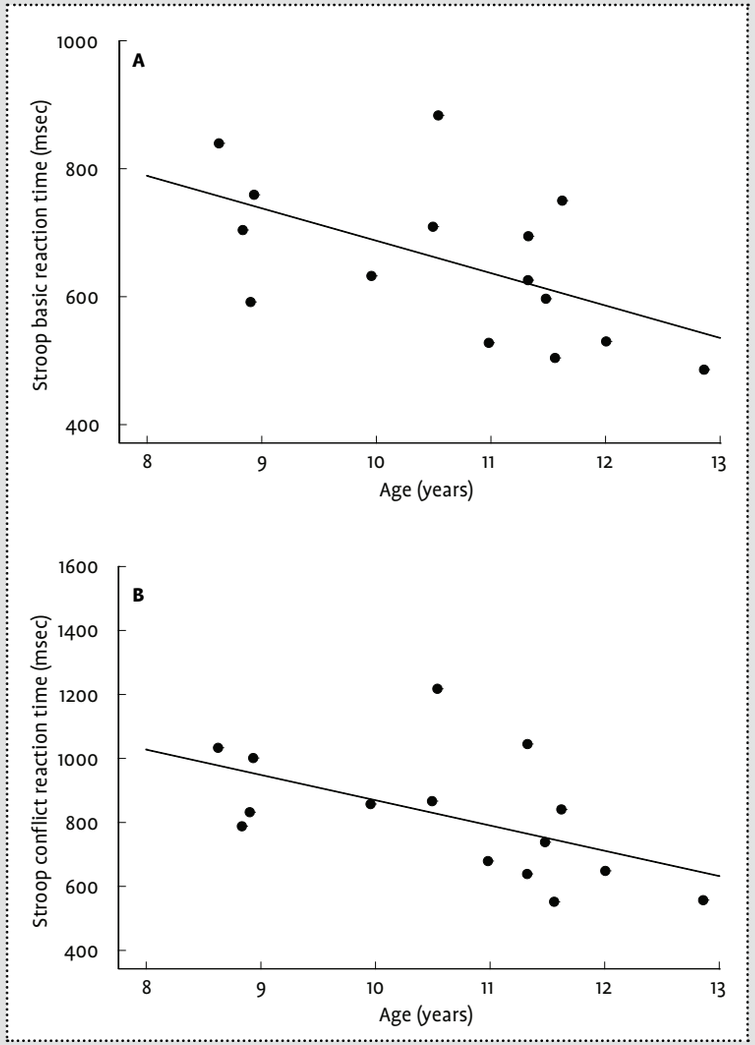
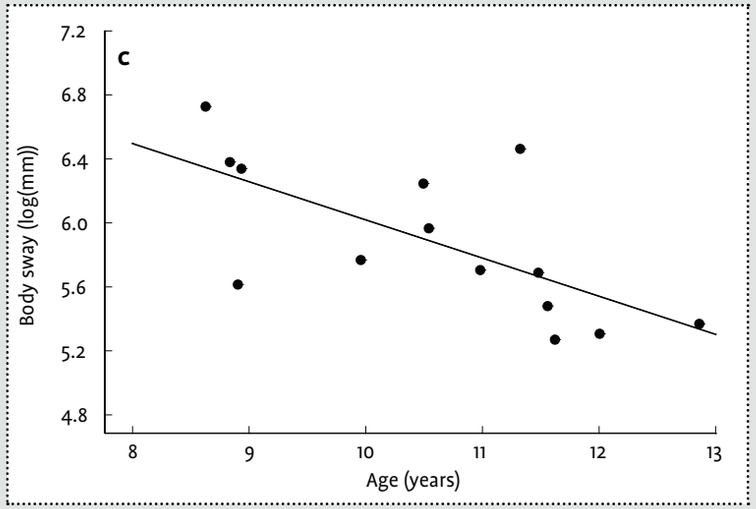


FIG. 1C



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