# Neuropsychological Outcome of Children Treated for Standard Risk Medulloblastoma in the PNET4 European Randomized Controlled Trial of Hyperfractionated Versus Standard Radiation Therapy and Maintenance Chemotherapy

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# Neuropsychological outcome of children treated for standard risk medulloblastoma in the PNET4 European randomised controlled trial of hyperfractionated (HFRT) versus standard radiotherapy (STRT) and maintenance chemotherapy.

Hugo Câmara-Costa, PhD[1†*], Anika Resch, MSc[2†], Virginie Kieffer, MSc[3], Clémence Lalande MSc[4], Geraldina Poggi, MD[5], Colin Kennedy, MBBS, MD[6,] Kim Bull, PhD[6,] Gabriele Calaminus, MD[7], Jacques Grill, MD, PhD[4], François Doz, MD[8], Stefan Rutkowski, MD[2], Maura Massimino, MD[9], Rolf-Dieter Kortman, MD[10], Birgitta Lannering, MD[11], Georges Dellatolas, MD, PhD[1], Mathilde Chevignard, MD, PhD[12] on behalf of the Quality of Survival working group of the Brain Tumour Group of SIOP-Europe.

[1] National Institute of Health and Medical Research, INSERM U669, Paris, France
[2] University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[3]Saint Maurice Hospitals, Saint Maurice, France
[4]Gustave Roussy, Villejuif, France
[5]Scientific Institute, IRCCS Eugenio Medea, Bosisio Parini, Lecco, Italy
[6]University of Southampton, Faculty of Medicine, Southampton, UK
[7]University of Muenster, Paediatric Oncology, Muenster, Germany
[8]Institut Curie and University Paris Descartes, Sorbonne Paris Cité, Paris, France
[9]Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
[10]University of Leipzig, Department of Radiation Therapy, Leipzig, Germany
[11]University of Gothenburg, Paediatric Oncology, Gothenburg, Sweden
[12] Saint Maurice Hospitals, Rehabilitation Department for children with acquired neurological injury; F-94410 Saint Maurice, France; and Sorbonne Universités, UPMC Univ Paris 06, Inserm, CNRS, LIB, F-7013 Paris, France
[†] Co-first authors
[*]Corresponding author

**Short running title:** Cognitive performance in the PNET4 study

**Reprint requests should be addressed to:** Hugo Câmara-Costa, INSERM U1178 (Secteur Jaune, porte 45, 1er étage), 16, avenue Paul Vaillant Couturier, 94807 Villejuif, France. Tel: (+33) (0)1 45 59 52 48; E-mail: hugocamaracostamail.com

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**Summary**

Cognitive performance (Intelligence Quotient) in children and young adults with standard risk medulloblastoma in the PNET4 randomised controlled treatment trial were compared between those allocated to hyperfractionated (HFRT arm) or standard radiation therapy (STRT arm), followed, in both treatment arms, by a standard chemotherapy regimen. Treatment with HFRT was associated with a trend towards better verbal outcomes in children aged less than 8 years at diagnosis, but no significant differences on the other cognitive measures.

**Abstract**

**Purpose/Objective(s)**: In the HIT-SIOP PNET4 European randomised controlled trial, children with standard risk medulloblastoma were allocated to hyperfractionated (HFRT arm, including a partially focussed boost) or standard radiation therapy (STRT arm) followed, in both arms, by maintenance chemotherapy. Event-free survival was similar in both arms. Previous work showed that HFRT arm was associated with worse growth and better questionnaire-based executive function, especially in children aged <8 years at diagnosis. Therefore, the aim of this study was to compare performance-based cognitive outcomes between treatment arms.

**Methods and Materials**: Neuropsychological data were collected prospectively in 137 patients. Using the Wechsler Intelligence Scales, Kaufman Assessment Battery for Children, and Raven's Progressive Matrices, we estimated: Full scale Intelligence Quotient (IQ) and, when available, Verbal IQ, Performance IQ, Working Memory Index (WMI), and Processing Speed Index (PSI).

**Results:** Among the 137 participants [HFRT arm n=71, STRT arm n=66, 63.5% males], mean (SD) age at diagnosis and assessment respectively was 9.3 years (3.2) (40.8% aged <8 years at diagnosis), and 14.6 years (4.3). Mean (SD) FSIQ was 88 (19) and mean intergroup difference was [95% CIs] 3.88 [-2.66 to 10.42, $p$=.24]. No significant difference was found in children aged >8 years at diagnosis. In children aged <8 at diagnosis, a marginally significant trend towards higher VIQ was found in those treated in the HFRT arm; a similar trend was found for PSI but not for PIQ, WMI or FSIQ (mean inter-group differences [95% CIs]): VIQ (12.02 [2.37 to 21.67]) $p$=0.02; PIQ (3.77 [-5.19 to 12.74]) $p$>.10; WMI (5.20 [-2.07 to 12.47]) $p$>.10; PSI (10.90 [-1.54 to 23.36]) $p$=.08; FSIQ (5.28 [-4.23 to 14.79]) $p$>.10.

**Conclusions**: HFRT arm was associated with marginally higher VIQ in children aged <8 years at diagnosis, consistent with the previous report using questionnaire-based data. However, overall cognitive ability was not significantly different.

**Key words**: child, medulloblastoma, PNET4, chemotherapy, radiotherapy, outcome, cognitive function, intellectual ability, verbal ability, perceptive reasoning, processing speed, working memory, quality of survival.

**Introduction**

Extensive research has consistently recognized longitudinal impairments associated with medulloblastoma (MB), the most frequent malignant brain tumour of the central nervous system (CNS) during childhood[1–3]. Standard treatment includes surgical resection, postoperative radiotherapy (RT) and adjuvant chemotherapy. Medulloblastoma survivors experience significant health-related problems, namely endocrine and growth morbidity and reduced fertility[4,5], second tumours[6], hearing loss[7], and long-term neurological deficits[8–10]. Among the major complications arising from the tumour and its treatment, predominantly radiotherapy and especially when given with chemotherapy, are the high rate of neurocognitive deficits, possibly attributable to the deleterious effects of radiation on white matter development[11,12]. MB survivors typically achieve scores below the mean of age-matched peers in measures of Intelligence Quotient (IQ), Verbal and Performance IQ, processing speed, working memory and sustained attention[13–16]. Importantly, deficits in these core cognitive domains tend to worsen over time[16–18]. To improve tumour control and quality of survival (QoS), hyperfractionated radiation therapy (HFRT) capitalizes on the fact that proliferating tumour cells are more sensitive than normal tissue to a given dose of radiotherapy if it is administered in a larger number of fractions of smaller size. This enhances the antitumour effects of radiotherapy while sparing normal tissues[19-22]. Compared with standard fractionated treatment (STRT), HFRT can be utilised either to maintain a given anti-tumour effect while decreasing unwanted effects on the CNS, or to increase the anti-tumour effect without increasing unwanted effects on the CNS. Previous uncontrolled studies of Carrie et al.[22] and Gupta et al.[23] reported higher post-treatment full-scale IQ in patients receiving twice-daily HFRT, compared to historical controls receiving once-daily STRT. However, using historical controls instead of a controlled experimental randomized design, limits the interpretation of these data.

Further, we could hypothesise that the lack of a significant IQ decline could be related to improved quality of posterior fossa irradiation, even in STRT, with less radiation to the temporal and occipital lobes.

The HIT-SIOP PNET4 phase 3 European randomized controlled treatment trial (RCT) for MB was designed to investigate the hypothesised biological advantage of HFRT over STRT. Five-year event-free survival was similar between the two arms[24]. A subsequent cross-sectional study assessed quality of

survival through questionnaires of executive function, health status, behaviour, health-related quality of life (HRQoL) and growth. This study[25] indicated significantly better executive functioning for children and young adults treated with HFRT compared with STRT, in accordance with Carrie et al.[22] and Gupta el al.[23]. No other significant advantage of HFRT was observed for health status, behaviour or HRQoL, and patients receiving HFRT had significantly greater deficit in height gain from diagnosis. The differences between treatment arms regarding executive functioning and growth impairment were significantly greater in patients aged less than 8 years at diagnosis[25]. The present study aimed to complement these findings by examining effects of HFRT and STRT on cognitive outcomes in PNET4 survivors as assessed directly using age-appropriate measures of intellectual ability.

**Methods**

**Patients**

A population of 338 participants (aged 4-21 years) from 10 countries was randomly assigned to either HFRT or STRT for M0 MB between 2001 and 2006.

STRT comprised 23.4Gy to the craniospinal axis and 54Gy to the posterior fossa given over 42 days in 30 daily fractions of 1.8Gy for 5 days per week. HFRT was given in 68 fractions: 1.0Gy twice per day with an 8-hour interval between fractions, given over 48 days. In the HFRT arm, the total craniospinal dose was 36 Gy, and the whole posterior fossa dose was 60 Gy, with a further focused boost of 8 Gy to the tumour bed. In both arms, a maximum of 8 doses of vincristine 1.5 $mg/m^2$ (maximum 2mg) was given once per week during radiotherapy, followed by adjuvant chemotherapy. Eight cycles of cisplatin 70 $mg/m^2$ intravenously, lomustine 75 $mg/m^2$ on day 1, and vincristine 1.5 $mg/m^2$ intravenously on days 1, 8, and 15, began 6 weeks after the end of RT, with a 6-week interval between each cycle[24].

The neuropsychological assessment was not part of the original PNET4 protocol, which comprised questionnaire assessments alone. Four of the original 10 participating countries had collected prospective or cross-sectional data regarding cognitive outcomes between 2004 and 2013. The 216 event-free patients from France, Germany, Italy and Sweden who remained in remission during the 9-month period of the cross-sectional follow-up study conducted by Kennedy and colleagues[25] were eligible for the present analyses and of these, 137 (63.4%) had data regarding cognitive outcomes

(71/107 [66.4%] HFRT; 66/109 [60.6%] STRT). A sub-group of 35 participants (25.5%, of 137) had had at least two assessments of the same cognitive outcomes (mean delay between evaluations 2.9 years). For this sub-group, the results of the last assessment were considered for the cross-sectional analyses.

**Procedure**

The present study conformed to ethical requirements of all participating countries. Written consent was obtained by the treating clinician to conduct cognitive assessments.

**Measures**

Cognitive measures differed according to participants' age and country. Patients were generally evaluated with age-appropriate Wechsler Intelligence Scales[26-29]. In Germany, age-appropriate Raven's Coloured and Standard Progressive Matrices[30, 31], the vocabulary subtests of the Wechsler Scales or Kaufmann Assessment Battery for Children[32] (K-ABC I/II, Riddles subtest) and the Number Recall test of the K-ABC I/II were used to assess children's performance, verbal and working memory abilities, respectively. Five measures of cognitive ability were derived from these assessments: Full Scale (FSIQ), Verbal IQ (VIQ) and Performance Intelligence Quotient (PIQ), as well as Working Memory (WMI) and Processing Speed Index (PSI, for France, Italy and Sweden only).

In addition, an adapted version of the Medical Examination form[33] addressed to the clinicians and information from the Medical Educational Employment and Social (MEES) questionnaire addressed to parents and adult participants[33] provided information on participant's baseline demographics and secondary outcomes.

**Statistical Analysis**

The effects of treatment allocation on the cognitive measures were evaluated through regression models: firstly, for the whole group and, secondly, by age category at diagnosis (<8 or ≥8 years), similarly to Kennedy and colleagues[25]. At each step, sex, interval between diagnosis and assessment, presence of post-operative complications (or, alternatively, presence of cerebellar mutism) was introduced in the regression models, together with treatment allocation.

Statistical significance testing was 2-tailed with a .003 significance level to adjust for multiple testing (Bonferroni correction). However, results with $p<.05$ and >.003 were categorised as of marginal

significance. For the longitudinal analyses, mean differences between first and second assessments were compared to zero using paired Student's t-tests.

## RESULTS

### *Group comparisons between participants and non-participants*

Participants with cognitive outcomes and non-participants were similar regarding sex, treatment allocation and interval between diagnosis and cognitive assessment. However, non-participants tended to be older at diagnosis (mean=11.89 vs. 9.31, $p<.01$) suggesting that older participants had a lower probability of receiving a cognitive assessment.

### *Demographic and baseline characteristics for participants*

Participants who received HFRT and STRT were similar regarding sex, age at diagnosis, age at assessment, and interval between diagnosis and assessment (Table 1). Regarding pre- and post-operative characteristics, the two groups were also similar except that a slightly higher rate of post-operative complications and extra ocular movement deficits was observed in participants receiving HFRT compared to those receiving STRT.

### *Cognitive outcomes at post-treatment evaluation for the whole group of participants*

The distribution of the five cognitive outcomes indicated considerable variability, with scores ranging from 40 to 145. Using a cut-off point of -2 standard deviations, 12.4%, of the FSIQ, 8% of VIQ, 12.5% of PIQ, 7% of WMI and 33.7% of PSI scores were in the lower extreme range.

Cognitive outcomes were similar according to sex, country, age at diagnosis, age at assessment, and interval between diagnosis and assessment. Mean scores tended to be lower ($p<.05$ in all cases) in the presence of post-operative ataxia: FSIQ (85.01 vs. 94.52), VIQ (89.76 vs. 99.4), WMI (89.34 vs. 95.29) and PSI (73.82 vs. 85.54). Post-operative cerebellar mutism was associated with lower mean PIQ (79.33 vs. 89.09) and PSI (65.83 vs. 81), and extra ocular movements deficits were associated with lower mean VIQ (90.37 vs. 98.27, $p<.05$ in all cases). The presence of any peri-operative complications, including cerebellar mutism, was also associated with lower mean scores of PSI (68.75 vs. 81.14, $p=.04$). No other differences were observed for the remaining post-operative characteristics. Due to these associations, the effects of peri-operative complications (or, alternatively, cerebellar mutism) were controlled for in the regression analyses described subsequently.

***Effects of treatment on cognitive outcomes***

Country by treatment interactions were not significant. In univariate analyses, all cognitive outcomes were similar between HFRT and STRT arms (Table 2). However, PSI tended to be higher in the HFRT arm (difference (95% CI) 7.9 (-.14 to 15.9), $p$=.05). In younger participants (<8 years at diagnosis) VIQ tended to be higher in the HFRT arm (difference (95% CI) 12.02 (2.4 to 21.7), $p$=.02). For the remaining measures, no other differences were observed between arms when age at diagnosis was considered.

The results of the regression analyses paralleled the univariate analyses described above. In the full sample, allocation to HFRT showed a marginally significant trend to higher PSI scores ($F$=4.74, $p$=.03) and in participants whose age at diagnosis was < 8 years it showed a marginally significant association with higher VIQ scores ($F$=7.1, $p$=.01). No other significant effect or strong trend associated with treatment allocation was found on the remaining cognitive outcomes, either for the total sample or for the sub-group of participants whose age at diagnosis was > 8 years. These same analyses were redone after exclusion of participants with peri-operative complications and cerebellar mutism and results remained unchanged.

***Longitudinal analyses***

Thirty-five participants (25.5% of 137) underwent two cognitive assessments. These participants were characterized by longer intervals between diagnosis and the last assessment ($p$=.01) and higher rates of cerebellar mutism ($p$=.03). None of the remaining baseline characteristics was different between participants with cognitive assessment performed at two time points and those who had data at one time point. The last assessment was performed at a mean interval from the first evaluation of 2.9 years, with the mean interval being similar in both arms.

Cognitive measures did not differ significantly between Time 1 and Time 2 (Table 3). However, there was a tendency for PIQ to increase from the first to the second assessment (difference (95% CI) 5.9 (1.1 to 10.7, $p$=.019).

Moreover, the difference between cognitive outcomes on the two occasions of testing (Time 2 minus Time 1) did not differ between HFRT and STRT arms (Table 4).

**DISCUSSION**

The results suggest that treatment allocation contributed to explain specifically the VIQ scores of participants aged less than 8 years at diagnosis. For this subgroup, those allocated to the HFRT arm had higher VIQ scores than participants in the STRT arm. Those allocated to HFRT also had a strong trend, falling short of statistical significance, to higher PSI scores in the reduced number of participants completing this test, both in the sample as a whole and in those aged less than 8 years at diagnosis. These effect sizes were large for VIQ and medium for PSI. Other differences between treatment arms for the remaining cognitive measures were small and non-significant. Longitudinal results, although unpowered, indicated no significant effects of treatment allocation on the cognitive outcomes, neither at Time 1 and Time 2, nor from the first to the second assessment.

In the present study, treatment was randomly allocated and follow-up rates for the cognitive assessment were reasonable (63%), which allowed the composition of two heterogeneous groups regarding IQ outcomes. However, some limitations should be taken into account. The measures used to assess cognitive performance differed according to country and, thus, might reflect distinct underlying constructs of cognitive ability. This limitation justifies caution in the interpretation of the results and generalization of these findings. Importantly, these results highlight the urgent need for an international consensus in the measures used to assess cognitive ability[34]. Moreover, participants were slightly younger at diagnosis than non-participants. However, this difference is not likely to have biased our results, since the only significant differences were observed for the subgroup of participants with younger age at diagnosis. Furthermore, the analysis per age category had not been planned in the initial protocol but was carried out in order to bring complementary information to confirm or refute the observation by Kennedy and colleagues[25] of benefits of HFRT to executive function. Finally, results of the regression analyses remained unchanged even when controlling for the marginally significant excess of peri-operative complications, namely cerebellar mutism in the HFRT arm.

The encouraging survival rates of patients treated for MB[24] has led researchers to focus on the long-term consequences of these tumours and their treatment on neurocognitive performance, most often focused on overall intellectual ability. Previous research has reported that MB survivors are at increased risk for cognitive impairment, with progressive IQ declines typically stabilizing within 1 to

2 standard deviations (SD) below the mean of typically age-matched developing peers 5 years after treatment[13,17,35,36]. The results of the present study align well with these prior reports. Collectively, the mean scores of all the survivors' IQ measures allocated either to STRT or HFRT arms fell 1 SD below the mean and approximately 10% of the participants evidenced performances 2 SD below the mean regardless of treatment. MB survivorship carries lingering effects on the patient's intellectual functioning with significant implication for other domains of QoS, namely academic achievement[36, 37]. An evidence-based conceptual model in which IQ deficits of MB survivors arise secondary to underlying impairments in core cognitive skills such as attention, processing speed and working memory[36, 37] has been proposed. The deficits observed in PSI for the full sample support this contention and suggest that these core cognitive skills might represent developmental precursors to overall delays in general cognitive ability. However, the considerable variability of FSIQ (range 40 to 140, 25% of survivors with IQ $\geq$ 100) implies that some patients do not follow the expected pathway of neurocognitive impairment in accordance with Palmer's conclusion[37].

PNET4 is the first RCT comparing IQ outcomes between patients who received HFRT versus STRT and this study aimed to explore further the effect of treatment on cognitive function recently reported by Kennedy et al. in PNET4 participants[25]. Our findings provide support for their observation that the effect of radiotherapy on executive function is moderated according to treatment because cognitive skills pertaining to information processing speed, working memory and attention represent the core developmental precursors of later intellectual and academic function[37].

Taken together with those of Kennedy et al. [25], our findings suggest that HFRT arm might result in more preserved cognitive function in children aged less than 8 years at diagnosis as suggested by previous reports of the greater vulnerability of these children to the adverse effects of treatment on neurocognitive outcomes[17, 36]. These results also parallel those reported by Carrie et al.[22] and Gupta et al.[23] that children treated with HFRT displayed more preserved cognitive functions when compared with historical controls. IQ deficits in MB survivors are probably due to a diminished ability to acquire new information, rather than the loss of previously acquired knowledge[15]. Applied to our results, the diminished impact of HFRT on young children's ability to acquire new information represents a plausible explanation for their superior VIQ scores, when compared with STRT. Moreover, we also

have to take into account that the difference between the two arms was not only the fractionation, but also the partially more focused boost in the HFRT arm, which could possibly have led to an increased protection of the temporal and occipital lobes. The more focused posterior fossa and primary site boost will most likely become a standard procedure[38].

Moreover, our results extend the findings reported by Kennedy and colleagues[25], who presented evidence that survivors allocated to HFRT arm evidenced better scores on the Behavior Rating Inventory of Executive Function (BRIEF) global executive composite score than the group that had received STRT. Interestingly, Vriezen and Pigott[39] reported a significant correlation between VIQ and the Metacognition index of the BRIEF questionnaire, i.e., the cognitive sub-scales of this questionnaire, in a group of children with traumatic brain injury. However, as argued by Kennedy and colleagues[25], although HFRT survivors obtained higher executive functioning scores than STRT survivors, self- or parental reports of behavioural adjustment, HRQoL or health status were comparable between treatment groups. As concluded by Chevignard and colleagues[40], although the use of questionnaires might complement information about executive functioning, they might rely on a more global frame of everyday functioning and provide less information regarding core cognitive processes. Further, in the previous study[25], HFRT survivors presented a greater decrement in height and reported more use of hearing aids. This difference in the use of hearing aids does not allow us to rule out the hypothesis that the better VIQ scores of young children allocated to HFRT could be attributed to more appropriate referrals to health services in case of hearing loss.

The longitudinal analyses indicated that IQ outcomes were not significantly different between the first and the second assessments, neither for the full sample nor for each treatment group. On one hand, these results follow the findings of Gupta et al.[23] who indicated the absence of any decreasing trend on measures of FSIQ, VIQ and PIQ for patients allocated to HFRT, when compared with historical controls. On the other hand, the results of the analyses performed with the full sample contrasts with an established body of literature documenting an IQ decline in MB survivors[22, 37], suggesting a possible overall improvement of MB treatments, regardless of radiotherapy fractionation, as suggested earlier regarding the protection of the temporal and occipital lobes. Nevertheless, our results should be interpreted with caution. The small number of patients with two available assessments collected

prospectively (mostly in two countries) coupled with the short time between assessment and diagnosis limited the ability of the study to detect clinically important differences between treatment arms, especially when considering subgroups according to the age at diagnosis.

In conclusion, this study provides some support to previous observations in the same RCT regarding possible benefits of HFRT, when compared to STRT in the PNET4 study, on young children's verbal ability. Although it does not demonstrate a clear advantage of HFRT in the regimen employed, that regimen, as comparison with STRT, was designed to be more effective on tumour cells and iso-effective in its effects on the CNS. The hypothesis that a lower dose regimen of HFRT, designed to be iso-effective on tumour cells with decreased adverse effects on the CNS, would bring clinically important benefits deserves further exploration with children aged less than 8 years at diagnosis being the group most likely to benefit. Further, this study reports detailed findings in patients treated with STRT, against which newer treatment approaches could be compared, such as lower CSI doses and a tumour bed rather than whole posterior fossa boost.

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Table 1

Descriptive statistics of the study's participants according to treatment allocation

| | HFRT | | | | STRT | | | |
|---|---|---|---|---|---|---|---|---|
| | *N* | *M* | *SD* | *Range* | *N* | *M* | *SD* | *Range* |
| *Demographic characteristics* | | | | | | | | |
| Age at diagnosis (years) | 71 | 9.1 | 3.23 | 4-17.6 | 66 | 9.5 | 3.14 | 4.3-17.3 |
| Age at diagnosis < 8 years, *n* (%) | 31 | (43.7) | | | 25 | (37.9) | | |
| Age at assessment [1] | 71 | 14.3 | 4.48 | 6.2-24.9 | 66 | 14.9 | 4.11 | 6.1-24.7 |
| Interval from diagnosis (years) | 71 | 5.2 | 2.81 | .08-9.9 | 66 | 5.4 | 2.53 | .58-10.5 |
| Males, n (%) | 46 | (64.8) | | | 41 | (62.1) | | |
| Premorbid developmental impairment, n (%) [2] | 2 | (2.8) | | | 4 | (6.1) | | |
| *Postoperative status* | | | | | | | | |
| Post-operative complications, n (%) [3] | 10 | (14.1) | | | 3 | (4.6) | | |
| Impaired consciousness, n (%) [4] | 0 | (0) | | | 2 | (3.1) | | |
| Impaired nerve III, n (%) [5] | 35 | (53) | | | 23 | (37.7) | | |
| Ataxia, n (%) [6] | 34 | (58.6) | | | 36 | (64.3) | | |
| Cerebellar mutism, n (%) [7] | 6 | (8.5) | | | 3 | (4.6) | | |

[†] Student's *t*-test; [††] Khi-2 de Mantel-Haenszel.

Table 2

Mean differences of cognitive outcomes according to treatment allocation and age at diagnosis.

| | HFRT | | | | STRT | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *N* | *M* | *SD* | *Range* | *N* | *M* | *SD* | *Range* | *p* † |
| FSIQ | 71 | 90.3 | 19.7 | 40-137 | 66 | 86.4 | 18.9 | 40- 122 | .24 |
| FSIQ (age > 8) | 40 | 90.7 | 21.8 | 40-137 | 41 | 87.6 | 19.3 | 40-118 | .49 |
| FSIQ (age < 8) | 31 | 89.7 | 16.8 | 65.5-128.5 | 25 | 84.5 | 18.6 | 40-122 | .27 |
| VIQ | 58 | 96.3 | 17.1 | 55-128 | 55 | 92.4 | 20.6 | 43-145 | .28 |
| VIQ (age > 8) | 31 | 95.8 | 17.4 | 55-128 | 34 | 97.1 | 22.1 | 47-145 | .79 |
| VIQ (age < 8) | 27 | 96.8 | 17.1 | 60-126 | 21 | 84.8 | 15.7 | 43-112 | .02 |
| PIQ | 70 | 89.7 | 21 | 40-140 | 66 | 87.1 | 17.1 | 40-122 | .43 |
| PIQ (age > 8) | 39 | 90.4 | 24.6 | 40-140 | 41 | 88.3 | 16.8 | 40-118 | .66 |
| PIQ (age < 8) | 31 | 88.9 | 15.8 | 65-128.5 | 25 | 85.1 | 17.7 | 41-122 | .40 |
| WMI | 68 | 92.3 | 13.8 | 55-124 | 61 | 89.1 | 15.3 | 55-120 | .21 |
| WMI (age > 8) | 38 | 90 | 14.8 | 55-124 | 39 | 88.6 | 16.1 | 56-120 | .69 |
| WMI (age < 8) | 30 | 95.2 | 11.9 | 65-118 | 22 | 90 | 14.2 | 55-110 | .16 |
| PSI | 29 | 83.3 | 14.7 | 50-112 | 28 | 75.4 | 15.5 | 50-100 | .05 |
| PSI (age > 8) | 18 | 81.1 | 15.6 | 50-112 | 17 | 75.1 | 16.3 | 50-100 | .27 |
| PSI (age < 8) | 11 | 86.8 | 13.1 | 62-103 | 11 | 75.9 | 14.8 | 50-96 | .08 |

† Student's *t*-test; FSIQ: Full Scale Intelligence Quotient; VIQ: Verbal Intelligence Quotient; PIQ: Performance Intelligence Quotient; WMI: Working Memory Index; PSI: Processing Speed Index.

Table 3

Time interval and difference in cognitive outcome scores between first and second assessments

| | **Time 2 - Time 1** | | | | |
|---|---|---|---|---|---|
| | *N* | *Mean* | *SD* | *Range* | $p^{\dagger}$ |
| Interval between assessment (yrs) | 32 | 2.9 | 1.8 | .92-7 | |
| FSIQ | 33 | .18 | 10.3 | -23-18 | .92 |
| VIQ | 34 | -1.7 | 13.7 | -31-25 | .47 |
| PIQ | 35 | 5.9 | 14.4 | -25-26 | .02 |
| PSI | 26 | -3.1 | 12.8 | -28-20 | .22 |

Nb. Due to missing data, WMI was not considered in these analyses; $^{\dagger}$ Paired student's *t*-test; FSIQ: Full Scale Intelligence Quotient; VIQ: Verbal Intelligence Quotient; PIQ: Performance Intelligence Quotient; PSI: Processing Speed Index.

Table 4

Mean comparisons of Time 1 and Time 2 cognitive outcomes by treatment allocation

| | **Time 1** | | | | | | **Time 2** | | | | | | **Time 2 - Time 1** | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **HFRT** | | | **STRT** | | | **HFRT** | | | **STRT** | | | **HFRT** | | | **STRT** | | | |
| | *N* | *M* | *SD* | *N* | *M* | *SD* | *N* | *M* | *SD* | *N* | *M* | *SD* | *N* | *M* | *SD* | *N* | *M* | *SD* | *p* [†] |
| FSIQ | 16 | 95.3 | 14.9 | 18 | 86.4 | 13.9 | 16 | 96.8 | 19.1 | 17 | 86.5 | 15.6 | 16 | 1.6 | 12.3 | 17 | -1.1 | 8.2 | .47 |
| VIQ | 16 | 103.6 | 15.1 | 18 | 90.8 | 15 | 16 | 101.2 | 17.8 | 18 | 89.7 | 20 | 16 | -2.4 | 15.1 | 18 | -1.1 | 12.8 | .78 |
| PIQ | 16 | 88.4 | 16.9 | 19 | 85.5 | 14.9 | 16 | 98.7 | 19 | 19 | 87.8 | 11.9 | 16 | 10.3 | 14.7 | 19 | 2.3 | 13.4 | .10 |
| PSI | 13 | 89.5 | 17.7 | 13 | 84.3 | 16.4 | 14 | 86.8 | 13.9 | 14 | 77 | 15.9 | 13 | -1.1 | 11.9 | 13 | -5.2 | 13.8 | .42 |

[†]Paired student's t-test.