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Reduced growth hormone secretion after cranial irradiation contributes to neurocognitive dysfunction

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ABSTRACT

The objective of this study was to investigate the relation between growth hormone (GH) and attentional electro-cortical responses to task-relevant stimuli (N2b), target detections, speed of responding, P300 latencies, and performance on neuropsychological tests in 19 patients who received external beam radiation therapy for brain tumors in adulthood. In addition, we studied the association between IGF-I and activation of the motor cortex responses (lateralized readiness potential, LRP).

Brain function was assessed using event-related potentials (ERPs) during a go/no go selective-attention task, including N2b, P300 and selective motor preparation as reflected in the LRP. Correlations were calculated between peak GH levels after a standardized growth hormone-releasing hormone (GHRH)–arginine test, plasma IGF-I, and cognitive functions. We separately studied four patients who were diagnosed with GHD according to the GHRH–arginine test.

Performance on WAIS digit span backward and the Rey–Osterrieth complex figure test correlated positively with GH peak. GHD patients performed worse than non-GHD patients on Stroop interference, trail making B/A attentional shifting and Rey–Osterrieth complex figure test. At trend-level significance, trails A performance was better in patients with lower GH levels and higher radiation doses, and GHD participants detected fewer targets in the go/no go selective attention task. N2b was not significantly altered by GH status. Furthermore, plasma IGF-I was positively correlated with the sum of digit span forward and backward. No relations with P300 were observed.

In this study only 21% (4/19) of the patients who received fractionated radiotherapy for a non-endocrine brain tumor were diagnosed with GHD. GHD in these patients was associated with impaired interference control, attentional shifting, and visual long-term memory. The results for interference control and attentional shifting suggest an additional effect of the radiation history.

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1. Introduction

Growth hormone (GH) deficiency (GHD) has often been associated with impaired psychological functions, and evidence is also emerging that a relationship exists between the GH-insulin-like growth factor-I (IGF-I) axis and cognitive function [1]. Although reduced GH secretion may directly affect cognitive function, it is also likely that subsequent attenuation of systemic or local IGF-I levels may be responsible for the observed effects [1,2].

A review and meta-analysis indicated that neuropsychological performance was impaired in adult GHD patients, predominantly in the domains of memory and executive functions, and that moderate improvements during GH therapy were found in particular also for these domains [2,3]. Studies of event related brain potentials (ERPs) offer support for underlying pathophysiological mechanisms. P300 latencies were found to be significantly prolonged in GHD patients and were significantly shortened after 6 months of GH therapy [4,5]. Furthermore, Lijffijt et al. [6] demonstrated reduced attention-related electro-cortical responses (N2b) to task-relevant stimuli in adults with childhood-onset GHD, which may reflect functional deficits in the cingulate cortex [7]. Previous research showed that the lateralized readiness potential (LRP), an ERP index for selective motor preparation, was smaller in elderly men with low IGF-I levels, indicating that both GH and IGF-I may contribute to the physiology of cognitive function [8].

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Long-term cognitive impairment is highly prevalent and burdensome in patients with brain tumors, possibly as a consequence of irradiation. However, adult patients with a low-grade glioma or meningioma who had been irradiated showed no additional detrimental effect by irradiation over damage by the tumor and by neurosurgery [9]. Shukitt-Hale et al. [10] found that cranial irradiation was associated with reduced performance in tasks assessing spatial learning and memory, which could at least partly be due to a lack of GH [11]. In the present study we report measures of cognitive functioning in relation to GH secretion, assessed by GH secretory capacity after GH releasing hormone (GHRH)–arginine, in patients who had previously undergone cranial irradiation for neurological tumors. Our hypothesis was that low GH secretion would be associated with reduced attentional electro-cortical responses to task-relevant stimuli (N2b), reduced accuracy of performance, slower speed of responding, increased P300 latencies, and impaired performance on neuropsychological tests of memory. For IGF-I we specifically predict an association with selective motor preparation (LRP) and speed of responding (reaction time). An additional comparison was made between patients with and without GHD, with respect to the measures mentioned previously.

2. Materials and methods

2.1. Subjects

We studied 19 patients (mean age 43.3 years, SD 10.6, range 30–69 years; 8 females; Table 1) who had received therapeutic cranial irradiation for primary brain tumors in adulthood. GH secretion was assessed using a standard GHRH–arginine test. Other pituitary hormones (cortisol, thyroid hormone, gonadal hormones) were either normal or had to be adequately substituted for at least 3 months. Four participants (mean age 49.3 years, SD 14.2, range 36–69 years; 1 female) who had a GH peaks lower than 9 μg/l after GHRH–arginine stimulation were diagnosed as GH deficient [12]. The other 15 participants (mean age 41.7 years, SD 9.3, range 30–62; 7 females) had an adequate GH response. We excluded participants with other neurological or psychiatric disease, other endocrine or internal disease, severe obesity (BMI > 32 kg/m^2), malnutrition (BMI < 18.5 kg/m^2), chronic alcohol or drug abuse, and use of medication that may affect cognitive functioning. There were no differences in radiation dose or tumor characteristics between GHD and non-GHD subjects. As expected, the GHD subjects had higher outcome measures of central obesity (BMI 27.7 ± 1.8 vs. 24.7 ± 2.5 kg/m^2, $p<.05$; waist 104.8 ± 6.9 vs. 86.4 ± 8.1 cm, $p<.01$).

The local medical ethics committee approved the study protocol. The study was approved by our local ethics committee, and conformed to The Code of Ethics of the World Medical Association (Declaration of Helsinki), printed in the British Medical Journal (18 July 1964). All subjects gave written informed consent.

2.2. Procedure

The GHRH–arginine test, which was performed according to standard procedures [12], took place in the morning. GHRH was obtained from Ferring (100 μg, Ferring Pharmaceuticals, The Netherlands). GH was measured using an immunometric technique on an Immulite Analyzer (Diagnostic Products, Los Angeles, CA). One microgram per liter corresponds to 2.6 mIU/l (WHO International Ref. Prep 80/505). IGF-I was measured using an immunometric technique on an Advantage Chemiluminescense System (Nichols Institute Diagnostics, San Juan Capistrano, CA).

In the afternoon of the same day, the ERP task (N2b, P300) and the neuropsychological tests were performed. All these tests were performed individually and under identical circumstances, in a sound-attenuated room.

2.3. Tasks

Standardized neuropsychological tests used were WAIS III digit span subtest, 15 word test, Rey–Osterrieth complex figure test, Stroop color–word task, trail making test A&B, Brixton spatial anticipation task, WAIS III symbol substitution subtest, WAIS III similarities subtest, verbal fluency N, A and animals and the Dutch adult reading test (Table 2). For detailed descriptions, the reader is referred to Nelson [13], Lezak [14], Aleman et al. [15], and Ball et al. [16]. Typical neuropsychological methods to assess selective attention are the Stroop color–word task (resistance against interference from distracting information), and the trail making task (shifting selective attention from one category to the other). ERPs were recorded during a go/no go selective-attention or 'selection-potential' task, as we have described previously [6,17].

2.4. Statistics

Bivariate Pearson correlations were calculated (two-tailed) using an SPSS® 12.0.1 for Windows between the peak GH level during the GHRH–arginine test, plasma IGF-I and all cognition outcome parameters (neuropsychological tests and ERP data). Furthermore, GHD-subjects were compared with non-GHD-subjects using an ANOVA.

3. Results

3.1. GH secretion and IGF-I

Mean peak GH in all subjects (Table 1) was 26.9 μg (range 2.4–96.2; SD 23.0), in the 4 GHD subjects 5.5 μg/l (range 2.4–8.1, SD 2.5) and in the non-GHD subjects 32.6 μg/l (range 9.6–96.2, SD 22.7). Mean plasma IGF-I levels for GHD and non-GHD subjects were respectively 134.3 (range 126–141, SD 6.7) and 130.8 ng/ml (range 93–206, SD 30.5). No significant correlation was found between GH peak and IGF-I.

3.2. Radiation

The mean radiation dose of all 19 patients was 55.1 Gy (range 45–60; SD 5.0). Patients received radiotherapy in daily fractions of 1.8 to 2.0 Gy. Except for two patients (Table 1, patient 9 and 14), the pituitary gland and hypothalamus could be fully shielded from the high dose planning target volume. Particularly in the patients with GHD, these endocrine organs at risk did not receive more than 30% (15–20 Gy) of the prescribed dose. The dose of total radiation did not differ between the GHD group (mean 58.3 Gy, range 54–60) and the non-GHD groups (mean 54.3 Gy, range 45–60). No significant correlations between radiation dose and GH peak were found ($p=.16$).

3.3. Neuropsychological tests

The 4 GHD patients performed significantly worse than non-GHD patients in all Stroop-test conditions (Fig. 1). Although, when separately analyzed, GHD and non-GHD subjects did not perform differently on trail making A (time in seconds needed to connect numbers) and trail making B (attentional shifting), a significant difference in trail making B/A ratio between the two groups was found ($p=.04$; Fig. 2). In addition, a positive trend-level correlation between trail making A score and GH peak ($r=.40$, $p=.09$) was observed. GHD subjects performed worse on the Rey–Osterrieth complex figure memory test, (as revealed by the ratio score, $p=.01$, Fig. 3a) and GH peak was positively correlated with the ratio score ($p<.01$; Fig. 3b). Furthermore, GH peak positively correlated with the WAIS III digit span backwards ($r=.46$, $p<.05$; data not shown).

Table 1
Characterization of individual patients. (To be published on journal website.)

Patient No.	Age (years)	Sex M/F	BMI kg/m^2	Waist (cm)	Diagnosis	Tumor localization	Radiation dose (Gray)	Radiation interval (months)	GH peak (μg/l)	IGF-I (μg/l)
1	36	M	25.5	112	Astrocytoma grade II	Right postcentral	60	91	2.4	126
2	43	M	27.5	97	Anaplastic mixed glioma	Left frontal	59	86	4.6	132
3	57	F	29.8	109	Meningioma	Left orbital/frontal lobe	54	50	6.9	138
4	49	M	27.8	101	Astrocytoma grade IV	Left frontal	60	68	8.1	141
5	32	F	27	83	Anaplastic oligo-astrocytoma	Temporo-occipital	60	28	9.6	145
6	35	M	26.3	99	Medulloblastoma	Left cerebellar	54	87	11.9	114
7	39	M	25.8	91	pinealoblastoma	Pineal gland	54	84	12.3	99
8	34	M	23.9	95	Germinoma	Pineal gland	45	51	13.8	165
9	62	M	27.4	92	Meningioma	Right cavernous sinus	54	16	23.5	105
10	41	F	29	86	Astrocytoma grade II	Left parieto-occipital	60	59	24.6	125
11	48	M	23.4	94	Astrocytoma n.o.s.	Right parietal	54	11	25	107
12	49	F	25.9	85	Astrocytoma n.o.s.	Right frontoparietal	60	87	25	116
13	46	F	25.1	92	Medulloblastoma	Cerebellum	54	45	26.2	206
14	42	F	25.8	81	Optic glioma	Left para/suprasellar with infrasellar extension	50	32	29.6	134
15	42	M	21.9	86	Oligodendroglioma grade II	Right frontoparasagittal	45	117	35.8	93
16	30	M	22.6	85	Astrocytoma grade IV	Posterior	60	98	46.2	133
17	62	F	26.0	68	Meningioma	Left frontotemporal	50	87	53.8	115
18	34	M	21.9	85	Medulloblastoma	Posterior fossa	54	68	55	170
19	34	F	20.2	74	Astrocytoma grade III	Left frontal	60	61	96.2	135

IGF-I reference levels: 30–35 years 90–275 (M), 92–280 (F); 36–40 years 85–250 (M), 85–260 (F); 41–50 years 74–220 (M), 75–220 (F); 51–60 years 64–200 (M), 65–200 (F); 61–70 years 58–175 (M), 60–170 (F).

IGF-I positively correlated with the total sum of the digit span forward and backward of the WAIS III ($r = .51$, $p = .03$; data not shown).

As to the other neuropsychological tests (Table 2), all other calculated differences between GHD and non-GHD patients as well as correlations between GH peak and test outcomes were not significant.

3.4. Selection potential task performance and ERPs

Mean target reaction time (MRT) was 433.4 ms (range 355.8–500.8, SD 39.6). Mean percentage targets detected was 98.6%. GHD participants detected somewhat fewer targets ($p = .06$). N2b amplitude was somewhat smaller for GHD patients, but this difference was not significant (data not shown). Mean reaction time (speed of responding) and P300 did not differ significantly between the GHD and the non-GHD group. (Fig. 4).

GH peak was not significantly correlated with percentage target detections, nor with correct rejections. Speed of responding (mean reaction time) on irrelevant trials, on which no response was wanted, correlated with GH peak ($r = .64$, $p = .05$, data not shown). No significant correlation was found between GH secretion and N2b. Selective motor preparation (LRP) was significantly correlated to IGF-I ($r = -.51$, $p = .03$). N2b was somewhat more negative when IGF-I levels were higher, but the correlation was not significant ($r = -.39$, $p = .095$). Plasma IGF-I did not correlate with percentage target detections, correct rejections nor with speed of responding.

4. Discussion

The present study has focused on pituitary function, with emphasis on GH secretion, in adults who had previously been irradiated during adulthood for intracranial tumors and on the relation between GH secretion and cognition. In particular, the focus was on the correlation between GH secretion and the performance on a variety of neuropsychological tests changes in GH secretion in relation to neurophysiological changes assessed by ERP.

The two main findings of this study are, first, that GHD was relatively rare (21% (4/19)) and secondly, that GHD in these patients was associated with an additional impaired cognitive functioning.

Only few studies have focused on pituitary function after cranial irradiation for non-pituitary tumors during adulthood. In a very recent meta-analysis by Appelman-Dijkstra et al. [18], only eight studies (published between 1976 and 2006) were included with 265 adults following brain irradiation for intracerebral tumors. In only four of these studies, the somatotropic axis was evaluated with different tests, mostly after irradiation and in one study also after surgery alone. The four studies show a prevalence of GHD after

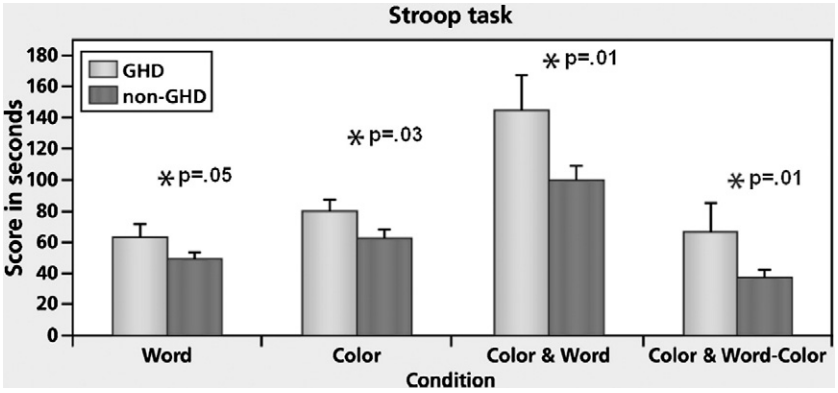

Fig. 1. Mean (±SD) performance in three Stroop-task conditions (GHD vs. non-GHD subjects). The rightmost part depicts the differences in the interference score (color–word minus color).

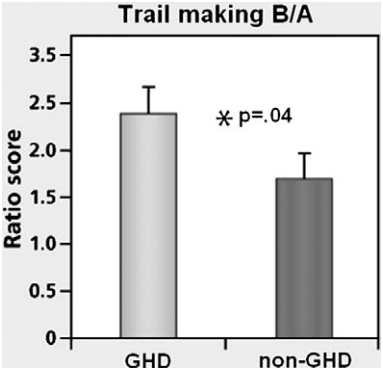

Fig. 2. Mean (±SD) performance on ratio score (TMT B/A).

surgery and irradiation varying between 27% and 50%. Our study population was comparable with the 56 patients studied by Agha et al. [19] who reported 32% of their patients having GHD. The difference may be explained by different use of GH stimulation tests (they used the insulin tolerance test (ITT) or a glucagon–arginine test). The difference in outcome shows the dilemmas about GH testing in these patients, and although hypothalamic damage may have occurred, the ITT is often contraindicated because patients with a history of brain tumors also often have a history of seizures. Darzy et al. [20] performed both an ITT and a GHRH–arginine test in 49 adults who had been irradiated mostly during childhood, and reported a significant correlation between the outcome of both tests, but a higher frequency of GHD when the ITT was used. However, it should be noted that for the diagnosis of isolated GHD, a second GH stimulation test is required, and the GHRH–arginine test is one of the best validated tests in patients with pituitary diseases [12]. Popovic et al. used the ITT and the GHRH-GH releasing peptide-6 test in a group of 22 adults who had been irradiated either during childhood or adulthood, and reported a defective GH releasable pool in 50% of their subjects, who were qualified as GHD by either of the tests [11]. When we analyze our data in this context, we feel that the four patients in our study who were diagnosed with GHD certainly qualify for this diagnosis, and should be offered GH substitution therapy, while patients with GH peak levels between 9 and 16.5 μg/l should be retested within a few years or if symptomatic.

A significant difference was found between the GHD and non-GHD group for delayed visual memory as assessed by the Rey–Osterrieth complex figure performance. This finding of an impaired delayed visual memory in GHD is consistent with that of an earlier report by Baum et al. [21]. In addition, we could demonstrate that a positive correlation exists between delayed visual memory and the GH peak in our entire study population, which may correspond with the presence of GH receptors in the hippocampus, and fits with previous studies reporting a general relation between GH and memory [3]. Significant differences were also found for several Stroop-task variables, the most important one being the color and word minus color difference score, which reflects the inverse of interference control, and indicates that GHD patients on average experienced more interference from incongruent color words when naming colors. In previous studies on childhood-onset GHD [22], no significant impairment in Stroop-interference control was observed and GH suppletion studies did not reveal effects on Stroop interference control [21]. In addition, the GHD patients in our study on average needed more time for trail making B, relative to A, while there was no correlation between trail making B performance and GH peak when we included the non-GHD subjects. As with Stroop interference, the previous study on childhood-onset GHD did not find any differences in trail making B attentional shifting [22], and GH therapy studies have failed to show beneficial effects on this variable [21].

A relevant point here may be the trend-level positive correlation between basic processing speed as assessed by trail making A, GH peak, and radiation dose. This essentially indicates better performance with lower GH levels; this is again in contradiction with our previous study [22], where childhood-onset GHD was associated with reduced trail making A performance. A related finding was reported by Peace et al. [23], who observed that GHD patients who had received radiation therapy in the past actually performed better on the trail making A than GHD patients without past radiation exposure, but that these radiation doses may be unfavorable for executive-function processes. This would explain why low GH was associated with impairments in interference control and attentional shifting in the present sample, but not for patients without a history of radiation therapy, as we reviewed previously [24].

In addition to the relationship between GH secretion and cognition after cranial radiotherapy, we assessed plasma IGF-I. A relation between IGF-I and short-term and working memory, as well as with central motor activation, which possibly differs from the relation between GH and cognition, was found. These data are in line with previous observations [15] and suggest a disruption between GH and IGF-I mediated effects after brain irradiation, similar to the previously reported effects of aging. The correlation between IGF-I and the LRP measuring selective motor preparation may be explained by the supportive effect of IGF-I for the myelin that surrounds the axons, and may fasten communication between neurons.

In conclusion, the present data on GH secretion and IGF-I, in a specific population of subjects exposed to brain irradiation, are

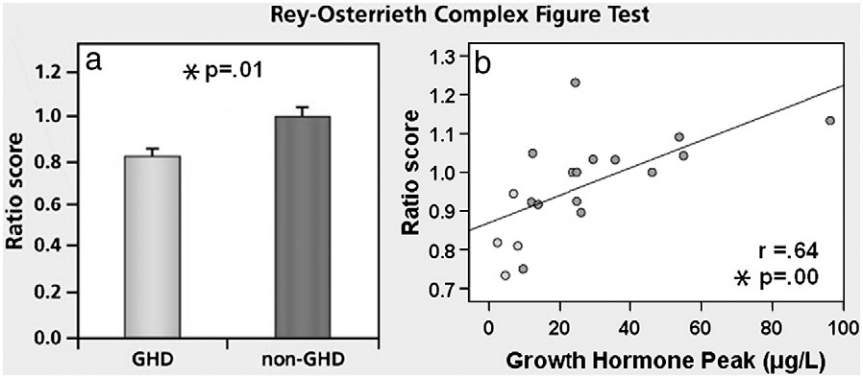

Fig. 3. Mean (±SD) ratio scores (delayed/immediate recall score) for the Rey–Osterrieth complex figure test (GHD vs. non-GHD subjects) (a) and significant correlation between GH peak and the ratio score (b).

Table 2
Neuropsychological assessment and results: correlation with IGF-I, GH peak and group difference (GHD).

Neuropsychological test	Putative cognitive function	Reference	IGF-I	GH peak	GHD
			r; *p*	*r*; *p*	*F*; *p*
Stroop color word task					
Word	Word reading	1	.15; .54	−.38; .11	4.44; .05
Color	Color naming	1	.06; .80	−.25; .30	5.89; .03
Color and word	Color naming and interference control	1	.11; .67	−.30; .21	10.64; .01
Color and word minus color	Interference control	1	.12; .64	−.28; .25	8.50; .01
Color/color and word	Interference control	1	−.15; .53	.14; .58	2.13; .16
Trail making task (TMT)					
Trail making task A	Processing speed, attention	2/3	.16; .51	.40; .09	1.22; .28
Trail making task B	Concept shifting	2/3	−.16; .51	.05; .84	.22; .64
TMT B minus A	Planning of movement and cognitive processing speed	4	−.33; .17	−.27; .27	2.41; .14
TMT B/A	Attentional shifting	5	−.26; .28	−.37; .12	5.14; .04
Rey–Osterrieth complex figure test					
Immediate recall score	Immediate visual memory	3	.32; .18	.43; .06	2.03; .17
Delayed recall score	Delayed visual memory	3	.21; .39	.61; .01	3.94; .06
Delayed/immediate recall score	Difference between delayed and immediate memory	3	−.50; .03	.64; .00	8.22; .01
Selective attention task					
Target detection	Sensory discrimination and selective attention	6	−.14; .58	.29; .22	3.94; .06
N2b (ERP)	Anterior (Fz) attentional process	6	−.39; .09	−.25; .30	2.17; .16
15 Word test (RAVLT)					
Recall score	Verbal memory	4	.09; .72	.19; .43	1.27; .27
Immediate recall score	Immediate verbal memory	2/3	.02; .94	.15; .53	.29; .60
Delayed recall score	Delayed verbal memory	2/3	.21; .38	.31; .19	2.06; .17
Recognition score	Recognition memory	3	−.39; .10	.15; .55	.79; .39
Verbal fluency					
Letter (N)	Language, executive function	3	−.19; .44	.08; .73	1.07; .32
Letter (A)	Language, executive function	3	−.24; .32	.03; .91	2.28; .15
Category animal	Language, executive function	3	−.02; .94	.05; .83	.98; .34
Brixton Spatial Anticipation Task	Spatial learning and working memory	7	−.16; .51	−.10; .69	1.48; .24
Dutch National Adult Reading Test	verbal intelligence	2	−.08; .73	.18; .46	1.29; .27
Wechsler Adult Intelligence Scale (WAIS)					
Digit symbol substitution	Cognitive and perceptual-motor processing speed	4	.01; .96	.15; .55	.46; .51
Similarities	Concept formation and abstract reasoning	3	−.19; .44	.16; .51	1.42; .25
Digit span					
Span forward	Short-term memory	2/3	.42; .07	.62; .01	.89; .36
Span backward	Short-term and working memory	2/3	.23; .34	.46; .05	1.04; .32
Span total		2/3	.51; .03	.39; .10	1.12; .31

1—Lansbergen (2007), 2—van Dam et al. (2006), 3—van Zandvoort et al. (2005), 4—Aleman et al. (1999), 5—new measure, 6—Ref. [17], 7—Shallice and Burgess (1996).

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consistent with other reports on memory deficits in subjects with low GH secretion and the association between selective motor activation and IGF-I. In contrast, reductions in interference control and attentional shifting as observed in the present GHD patients are quite discrepant from previous reports and may rather reflect radiation effects.

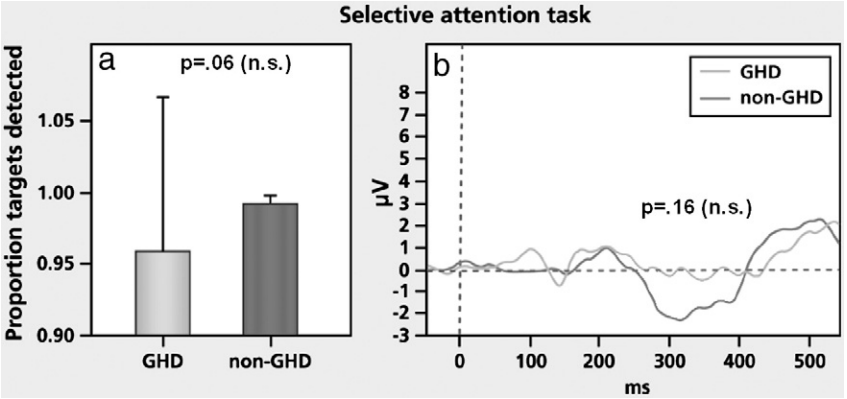

Fig. 4. Mean (±SD) proportion of targets detected (GHD vs. non-GHD subjects) during the selective attention task (a) and mean activity area 280–400 ms (N2b) over anterior cortical areas (Fz) (b). No significant differences between GHD and non-GHD were observed.

Conflict of interest statement

All authors state that there are no financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work, all within years of beginning the work submitted.

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