

Assessment of neurocognitive function in association with WHO grades in gliomas

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Declaration of Interest

The authors report no declaration of interest. All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as consultancies; employment; advocacy groups; grants or funding; fees and honoraria; patent applications / registrations; royalties; stock or share ownership; paid expert testimony), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

List of abbreviations

World Health Organization (WHO), Neurocognitive function (NCF), Wechsler Adult Intelligence Scale-Third Edition (WAIS-III), Wechsler Memory Scale-Revised (WMS-R), Karnofsky performance status score (KPS), World Health Organization (WHO), Isocitrate dehydrogenase 1 (IDH1), Full-Scale Intelligence quotient (FSIQ), Verbal Comprehension Index (VCI), Perceptual Organization Index (POI), Working Memory Index (WMI), Processing Speed Index (PSI), Verbal Memory (VeM), Visual Memory (ViM), Memory quotient (MQ), Attention/Concentration (At/Co), Delayed Recall (DeR), Standard Error of Measurement (SEM)

Abstract

Objective: High-grade gliomas are fast-growing and may exhibit more severe neurocognitive function (NCF) decline compared with low-grade gliomas. A comprehensive understanding of the NCF in patients with glioma may be critical for developing effective glioma treatments and rehabilitation interventions. This study evaluated NCF more comprehensively in patients with glioma using the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) and the Wechsler Memory Scale-Revised (WMS-R), and also determined the differences in NCF in relation with the WHO grades of gliomas.

Methods: Thirty-five patients with newly diagnosed glioma were reviewed in the present study. The patients were divided into three groups, Grade II, III, and IV, based on the World Health Organization's classification of tumors of the central nervous system. NCF was assessed using the WAIS-III and WMS-R.

Results: There were 14 (40.0%), 7 (20.0%), and 14 (40.0%) patients in the grade II, grade III, and grade IV groups, respectively. The results of the Kruskal-Wallis test showed significant differences in all the scores of the WAIS-III and WMS-R between grade II and grade IV. The scores of the WAIS-III and WMS-R in grade IV patients were borderline for NCF disorders, except in the attention/concentration domain. On the other hand, grade II and III groups had normal scores.

Conclusion: Therefore, patients with a grade IV glioma presented NCF decline compared to grade II and III glioma. In contrast, the results of the WAIS-III and WMS-R indicated that the NCF of patients with grades II and III glioma was intact.

Keywords: glioma, grade, neurocognitive function, WAIS-III, WMS-R

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Introduction

Gliomas are the most common primary central nervous system tumors. Gliomas generally disrupt brain function through the destruction of brain tissue, compression, displacement, and ischemia [1]. Consequently, patients with glioma often exhibit impaired neurocognitive function (NCF), including

attention, memory, executive functions, language, visuoconstructive abilities, and processing speed [1,2,3]. Additionally, most patients with glioma present some decline in NCF in the early stage of the disease before treatment [4, 5].

NCF is an essential predictor of survival in patients with glioma [6, 7]. It is also linked with independent daily living and social participation. Therefore, a more detailed assessment of NCF is required to treat patients with glioma effectively.

High-grade gliomas are fast-growing and may cause more severe NCF impairment compared with low-grade gliomas [8]. Previous studies have reported that the WHO grades of gliomas affect NCF in patients with glioma [1, 8, 9, 10]. On the other hand, some studies have reported that the WHO grades are not clearly related to cognitive performance in patients with glioma [11, 12]. Therefore, a change of NCF in relation to the grade of glioma still remains unclear. It is essential to determine the characteristics of NCF in relation to the WHO grades of gliomas to provide more suitable rehabilitation to patients with glioma.

The Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) and the Wechsler Memory Scale-Revised (WMS-R) are comprehensive neuropsychological evaluation instruments with high reliability and validity for detecting minimal changes in NCF. One neuropsychological study using the WAIS-III reported that patients with brain tumors had significantly lower performances after surgery than healthy matched controls [13]. However, the literature lacks information regarding comprehensive assessment of NCF in patients with glioma using the WAIS-III and WMS-R.

This study comprehensively investigated NCF in patients with glioma retrospectively using the

WAIS-III and WMS-R and also examined whether the NCF differed depending on the WHO grades of gliomas.

Materials and Methods

Patients

We retrospectively reviewed all the clinical (age, sex, dominant hand, Karnofsky performance status score (KPS) [14], seizure history, and antiepileptic therapy) and histological records of 142 patients with glioma who were admitted to the Kyoto University Hospital's Department of Neurosurgery between 2016 and 2019. Then, we selected 36 patients with newly diagnosed glioma who had enough time before the glioma treatment to undergo neuropsychological assessment using the WAIS-III and WMS-R. One patient was excluded from the study because of the history of the cavernous hemangioma with open surgical resection. Other patients had no history of other neurological or psychiatric diseases, radiotherapy, or chemotherapy before the completion of testing, with the exception of receiving antiepileptic therapy for seizure disorder secondary to glioma. In all, 35 patients with glioma (17 females, 18 males) were included in this study (see Table 1). All histological reports were reviewed according to the 2016 World Health Organization (WHO) classification of tumors of the central nervous system [15]. Using grades of the WHO classification of tumors, patients were classified into three groups, including grade II, grade III, and grade IV.

As genetic information of glioma, mutation status of the isocitrate dehydrogenase 1 (IDH1) and 1p/19q codeletion was recorded in this study. A previous study has reported methods of performing IDH1

immunohistochemistry to assess the genetic mutation status [16]. A neurosurgeon and radiologist reviewed MRI scans of the identified lesion hemisphere and glioma region of patients before treatment.

The ethics committee of Kyoto University Graduate School and Faculty of Medicine (R1515) approved the study procedures. The procedures were performed in accordance with the Declaration of Helsinki. This study conforms to all the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. All patients were informed about the study procedures and provided written informed consent before participation.

Evaluation of Neurocognitive Function

A comprehensive neuropsychological evaluation was conducted by licensed occupational or speech therapists. The neuropsychological evaluation included the WIAS-III and WMS-R. The WAIS-III provided the following outcomes: a full-scale intelligence quotient (FSIQ) as well as group index scores for verbal comprehension index (VCI), perceptual organization index (POI), working memory index (WMI), and processing speed index (PSI). The WMS-R provided a memory quotient (MQ) as well as index scores for verbal memory (VeM), visual memory (ViM), attention/concentration (At/Co), and delayed recall (DeR). The neuropsychological evaluation typically required approximately three hours to complete. These tests were administered before surgical resection of glioma, radiotherapy, or chemotherapy. The effect of antiepileptic therapy was not investigated.

Statistical Analysis

The normality of the data was evaluated using the Shapiro-Wilk test. For group comparisons, this study used the Kruskal-Wallis test for nonparametric data and a one-way analysis of variance for

parametric data. Parameters showing significant differences in the Kruskal-Wallis test or one-way analysis of variance were subjected to the Steel-Dwass multiple comparison test. Concerning the scores showing a significant difference in the Steel-Dwass test of WAIS-III and WMS-R, the Standard Error of Measurement (SEM) was also compared in this study. The SEM was calculated using the following formula: $SEM = SD \sqrt{1 - r}$, where r denotes the intraclass correlation coefficients reported by Wechsler [17, 18]. The χ^2 test was used to examine sex differences, dominant hand, seizure history, antiepileptic therapy, IDH1 mutation status, 1p/19q codeletion, and lesion hemisphere between the three groups. All statistical analyses were performed using SPSS for Windows Version 17.0 (SPSS Inc, Chicago, IL), and p -values less than 0.05 were considered statistically significant.

Results

Patient Characteristics

This study included 14 patients (40%) in grade II glioma (Oligodendroglioma, IDH mutant and 1p/19q codeleted: 5; Oligodendroglioma, NOS: 1; Diffuse astrocytoma, IDH mutant: 4; Diffuse astrocytoma, IDH wild-type: 2; Diffuse astrocytoma, NOS: 1; Central neurocytoma, NOS: 1), 7 patients (20%) in grade III glioma (Anaplastic oligodendroglioma, NOS: 1; Anaplastic astrocytoma, IDH mutant: 2, Anaplastic astrocytoma, IDH wild-type: 1; Anaplastic astrocytoma, NOS: 1, Diffuse astrocytoma, IDH wild-type: 1, Anaplastic glioma, IDH wild-type: 1), and 14 patients (40%) in grade IV glioma (Glioblastoma, IDH mutant: 2, Glioblastoma, IDH wild-type: 14).

Table 1 shows the patients' age, sex, dominant hand, KPS, seizure history, antiepileptic therapy,

histology, IDH1 mutation status, 1p/19q codeletion, lesion hemisphere, and glioma region. The differences in sex, antiepileptic therapy, 1p/19q codeletion, and lesion hemisphere were not significant between groups. There was a significant difference in the age between grade II and grade IV ($p = 0.034$) groups. Grade II patients were younger than grade IV patients. There was a significant difference in the KPS between grade II and grade IV ($p = 0.019$) groups. Grade IV patients were worse than grade II patients. The dominant hand was not independent between groups ($\chi^2 = 8.891, p = 0.012$). There was a significant difference in the seizure history ($\chi^2 = 10.535, p = 0.005$). A higher number of grade IV patients had no seizure history. There was a significant difference in the genetic mutation status ($\chi^2 = 14.844, p = 0.005$). The presence of IDH1 mutation (IDH1 R132 positive) was higher than the absence of mutation (IDH1 R132 negative) among grade II patients. Conversely, IDH1 R132 negative was more prevalent than IDH1 R132 positive among grade IV patients. Frontal gliomas (grade II: 21.4%, grade III: 28.6%, grade IV: 21.4%), temporal gliomas (grade II: 14.3%, grade III: 0%, grade IV: 21.4%), insular gliomas (grade II: 21.4%, grade III: 28.6%, grade IV: 0%), and parietal gliomas were found in each group (grade II: 14.3%, grade III: 14.3%, grade IV: 0%). Gliomas in other regions were also found in each group (grade II: 28.6%, grade III: 28.6%, grade IV: 57.1%).

(Table 1 Here)

Neurocognitive Performance before Glioma Treatment

Table 2 and figure 1 and 2 show the scores of the evaluation of neurocognitive function of the three groups. The result of the Kruskal-Wallis test showed significant differences in the FSIQ. Furthermore, the results of the Steel-Dwass test for multiple comparisons showed that the FSIQ was significantly higher in

the grade II group compared to the grade IV group ($p = 0.0001$). The FSIQ was also significantly higher in the grade III group compared to the grade IV group ($p = 0.0262$). The difference in the FSIQ scores between the grade II and grade IV groups and between the grade III and grade IV groups was larger than the SEM (SEM = 2.45). According to the results of the Kruskal-Wallis test, the VCI, POI, WMI, and PSI were significantly different between the groups. Furthermore, the results of the Steel-Dwass test for multiple comparisons showed that the VCI, POI, and PSI were significantly higher in the grade II group compared to the grade IV group (VCI: $p = 0.0356$, POI: $p = 0.0024$, PSI: $p = 0.0109$). The difference in the VCI, POI, and PSI scores between grade II and grade IV groups was larger than the SEM (VCI: SEM = 3.53; POI: SEM = 4.68; PSI: SEM = 4.51). The WMI was significantly higher in the grade II group compared to the grade IV group ($p = 0.0065$). The WMI was also higher in the grade III group compared to the grade IV group ($p = 0.0207$). The difference in the WMI scores between the grade II and grade IV groups and between the grade III and grade IV groups was larger than the SEM (SEM = 4.11).

The result of the Kruskal-Wallis test showed significant differences in the VeM, ViM, MQ, At/Co, and DeR. According to the results of the Steel-Dwass test, the VeM, ViM, and At/Co were significantly higher in the grade II group compared to the grade IV group (VeM: $p = 0.0019$; ViM: $p = 0.0002$; At/Co: $p = 0.0019$). The difference in the VeM, ViM, and At/Co scores between grade II and grade IV groups was larger than the SEM (VeM: SEM = 6.79; ViM: SEM = 5.31; At/Co: SEM = 6.95). The MQ and DeR scores were significantly higher in the grade II group compared to the grade IV group (MQ: $p = 0.0001$; DeR: $p = 0.0004$), and in the grade III group compared to the grade IV group (MQ: $p = 0.0321$; DeR: $p = 0.0474$). The difference in the MQ and DeR scores between the grade II and grade IV groups and between

the grade III and grade IV groups were larger than the SEM (MQ: SEM = 5.81; DeR: SEM = 5.41).

(Table 2 and figure 1 and 2 Here)

Discussion

In this study, we performed a comprehensive evaluation of NCF in patients with glioma using the WAIS-III and WMS-R and also investigated the difference in NCF in relation to the WHO grades of gliomas. The most important finding of the present study is that the scores of patients with grade IV glioma were significantly lower than that of grade II and III patients. In contrast, all the scores of the WAIS-III and WMS-R of grade II and III group were higher than 90 with two-thirds SD, indicating that the patients with grade II and III glioma were cognitively intact. These results were quite unexpected since the previous studies have reported that patients with a high-grade glioma showed NCF impairment compared to a low-grade glioma [1, 9]. Previous study has also reported that the median survival time of patients with grade III and IV glioma were 26 and 13 months, respectively [19]. There is obvious difference of clinical characteristics, thus, it is predicted that there are a high possibility the differences of neurocognitive functions between grade III and IV glioma. Therefore, this result suggests that dividing the patients into three groups of grade II, III, and IV rather than high-grade and low-grade might be more appropriate to determine the relationships between tumor grades and NCF in patients with glioma. On the other hand, the issue regarding classification of grade seems to be remaining because the sample-size in the present study is small, especially in grade III.

Memory performance, including delayed recall, is often used as an outcome measure following brain

tumor treatment [20]; however, it remains unclear which domains of memory function are most likely to be affected by high-grade gliomas. In this study, the delayed recall scores of grade IV patients were lower than 70 points, thus they were diagnosed with cognitive impairment. Our study is the first to report that delayed recall in grade IV disease patients showed a marked decrease using the WMS-R. Furthermore, grade IV patients scored below 85 in the WAIS-III, which is defined as the borderline for NCF disorders. Koehler et al. have reported that delayed recall affects activities of daily living, such as one's own medication [21]. Hsieh et al. [22] have also reported that the personal performance score was strongly correlated with the verbal memory, visual memory, general memory, and delayed recall indices of the WMS-R. Moreover, one neuropsychological study has reported that scores of the FSIQ and MQ are an indicator for returning to work under the conditions of competitive employment [23]. In view of these previous and present findings, it is essential to evaluate more carefully the effects of NCF on daily life and social participation of grade IV patients after treatment.

One study has reported that the NCF improved after surgery [24]. Cognitive rehabilitation is now considered an alternative treatment approach. Some studies showed improvements in NCF in patients with traumatic brain injury, stroke and Alzheimer's diseases who underwent cognitive rehabilitation [25, 26]. Gehring et al. [27] have also reported that cognitive rehabilitation contributes to improve NCF, such as verbal memory, in patients with glioma. A previous study has also reported that neuropsychologic testing improved after low-grade glioma resection [28]. Therefore, for patients with grade IV, if NCF decline impairs independence in daily life or social participation after treatment, appropriate rehabilitation intervention may be required. However, this study did not include changes after treatment and

rehabilitation intervention, thus a longitudinal study on whether rehabilitation improves cognitive decline in patients with grade IV should be considered. According to the study results, the grade IV group showed the lowest scores in all domains of the WMS-R, especially in delayed recall. These results are consistent with those reported by Posti et al. [10]. Additionally, a negative rate of IDH1 mutation status in this study was the highest in the grade IV group. Previous studies have reported that the biomolecular effect by the glioma, including IDH1 mutation status, has a strong possibility of progressing to NCF decline in patients with glioma [29, 30, 31]. Our data supports the suggestion of these previous studies on NCF decline in patients with glioma.

In the present study, age of the grade IV group was significantly higher than the other two groups. NCF is generally affected by age [32]. However, we did not need to consider the age because the WAIS-III and WMS-R have age-corrected stratified norms at nine age levels.

The present study has some limitations. First, IQ and index scores of the WAIS-III are affected by the education level [33]. However, information regarding the patient's education level was unclear in this study. Second, a previous review article has reported that preoperative glioma volume correlated significantly with the risk of impairments in NCF [29]. However, the location and volume of the glioma were not considered in this study. Third, this was a cross-sectional study. A longitudinal study will be required since high-grade glioma patients show a fairly rapid decline as compared to those with low-grade gliomas. Finally, the sample size was small in the grade III group.

Conclusion

The results of this study indicated that patients with a grade IV glioma exhibited NCF decline, especially delayed recall, whereas the NCF of patients with grade II and III were intact, according to the WAIS-III and WMS-R results. This result suggests that it is important to evaluate NFC more carefully and to consider the impact of NCF decline on their daily life and social participation, especially in patients with grade IV.

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Availability of data and material

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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Figure Legends

Figure 1. Result of WAIS-III by the WHO grades in gliomas.

In the box plots, the boundary of the box closest to Zero indicate the 25 th percentile, a block line within the box marks the median, and the boundary of the box farthest from zero indicates the 75 th percentile. Whiskers above and below the box indicate the 10 th and 90 th percentiles.

(A) Full-Scale Intelligence quotient (FSIQ), (B) Verbal Comprehension Index (VCI), (C) Perceptual Organization Index (POI), (D) Working Memory Index (WMI), (E) Processing Speed Index (PSI)

Figure 2. Result of WMS-R by the WHO grades in gliomas.

For explanation of box plots see Figure 1 legend.

(A) Verbal Memory (VeM), (B) Visual Memory (ViM), (C) Memory quotient (MQ), (D) Attention/Concentration (At/Co), (E) Delayed Recall (DeR)

Table 1. Participant characteristics

	Glioma Grade			P
	II (n = 14)	III (n = 7)	IV (n = 14)	
Age, y, Mean (SD)	41.9 (14.6)	48.9 (14.2)	56.7 (13.5)	0.044
Sex (female, male), n	5, 9	4, 3	8, 6	0.462
Dominant hand (Right, Left), n	13, 1	4, 3	14, 0	0.012
KPS, Mean (SD)	97.1 (5.9)	91.4 (9.9)	82.9 (17.1)	0.019
Seizure history, n (%)	10 (71.4)	6 (85.7)	3 (21.4)	0.005
Antiepileptic therapy, n (%)	12 (85.7)	7 (100)	14 (100)	0.204
Histology, n (%)				
Glioblastoma	-	-	14 (100)	
Oligodendric tumor	6 (42.9)	1 (14.3)	-	
Astrocytic tumor	7 (50)	5 (71.4)	-	
Central neurocytoma	1 (7.1)	-	-	
Anaplastic glioma	-	1 (14.3)	-	
IDH1 mutation status (Positive, Negative, Atypical), n	11, 2, 1	3, 4, 0	2, 12, 0	0.005
1p/19q codeletion (Positive, Negative, No-data), n	7, 5, 2	6, 0, 1	12, 1, 1	0.152
Lesion hemisphere (Right, Left), n	7, 7	3, 4	7, 7	0.944
Tumor region (Right, Left), n				
Frontal	3 (0, 3)	2 (1, 1)	3 (1,2)	
Temporal	2 (2, 0)	0	3 (2,1)	
Insular	3 (2, 1)	2 (1,1)	0	
Parietal	2 (1, 1)	1 (0,1)	0	
Other	4 (2, 2)	2 (1, 1)	8 (4, 4)	

KPS; Karnofsky performance status score

Age and KPS calculated using Kruskal-Wallis test.

Number of female and male, dominant hand, seizure history, Antiepileptic therapy, IDH1 mutation status, 1p/19q codeletion, lesion hemisphere calculated using χ^2 test.

Table 2. Comparison of cognitive functions in the three groups

	Glioma Grade			P
	II (n = 14)	III (n = 7)	IV (n = 14)	
	Mean (SD)	Mean (SD)	Mean (SD)	
Intelligence				
WAIS-III				
FSIQ	105.4 (11.9)	102.3 (20.5)	77.9 (12.7)	0.0001
Verbal comprehension index	102.6 (10.9)	100.6(17.5)	84.5 (18.6)	0.0386
Perceptual organization index	106.2 (16.2)	101.3 (19.8)	80.3 (16.1)	0.0037
Working memory index	103.7 (13.1)	106.4 (23.6)	82.5 (16.4)	0.0025
Processing speed index	101.4 (14.7)	92.7 (20.5)	80.5 (21.5)	0.0188
Memory				
WMS-R				
Verbal memory	105.1 (15.5)	94.3 (20.3)	76.5 (16.2)	0.0019
Visual memory	107.8 (10.6)	97.7 (20.6)	78.2 (16.3)	0.0003
Memory quotient	106.7 (14.5)	94.9 (21.6)	73.3 (11.0)	0.0001
Attention/Concentration	113.2 (13.7)	103.3 (19.9)	88.6 (17.2)	0.0027
Delayed recall	104.6 (16.5)	94.0 (22.9)	68.8 (14.2)	0.0005

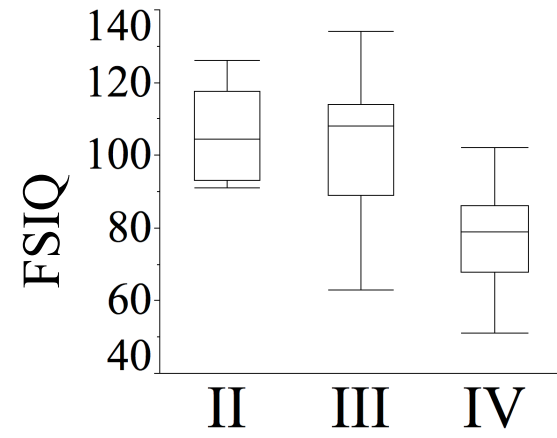
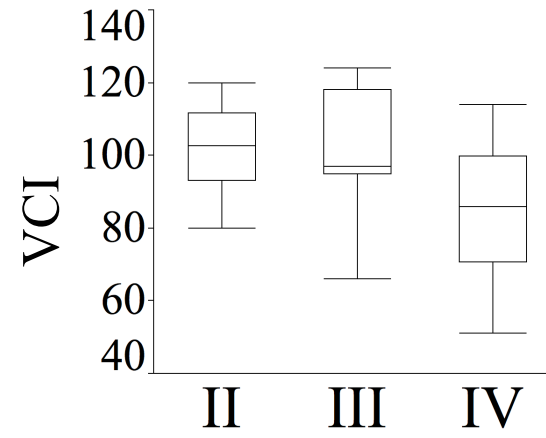
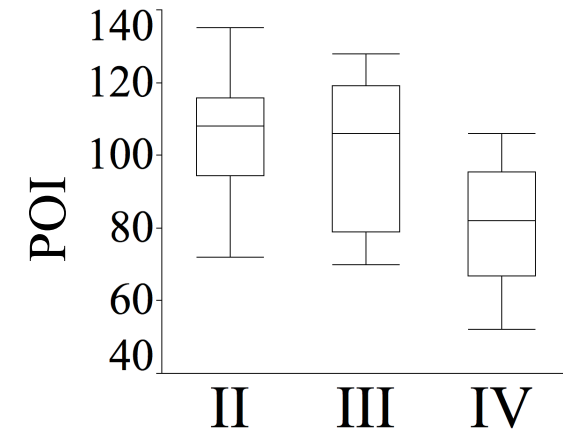
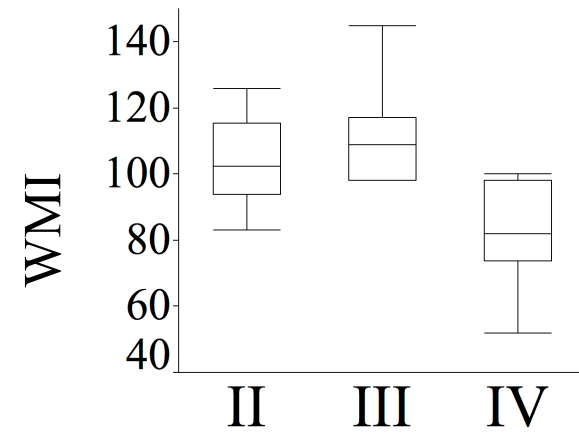
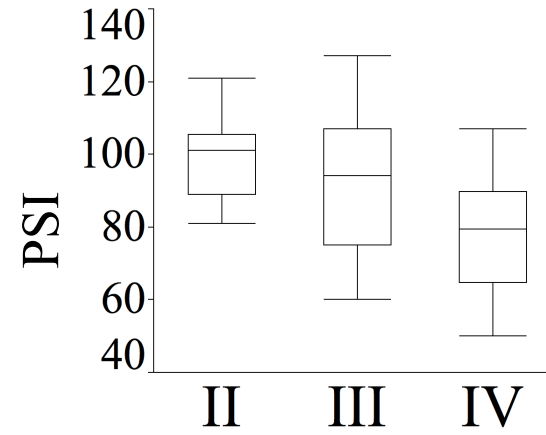
WAIS-III; Wechsler Adult Intelligence Scale third Edition

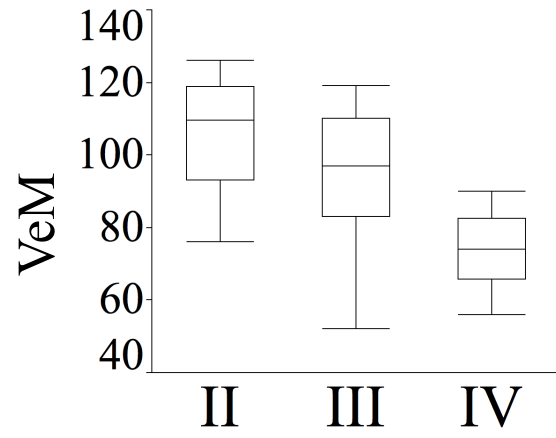
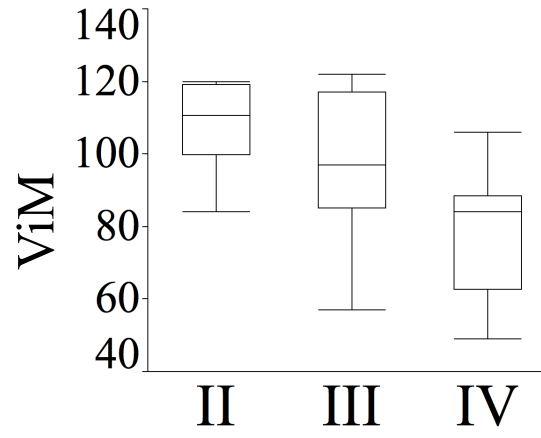
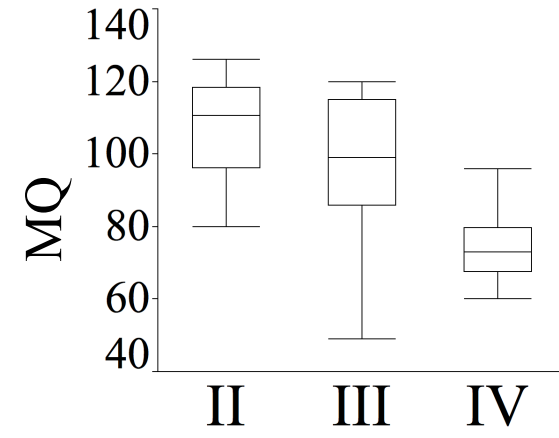
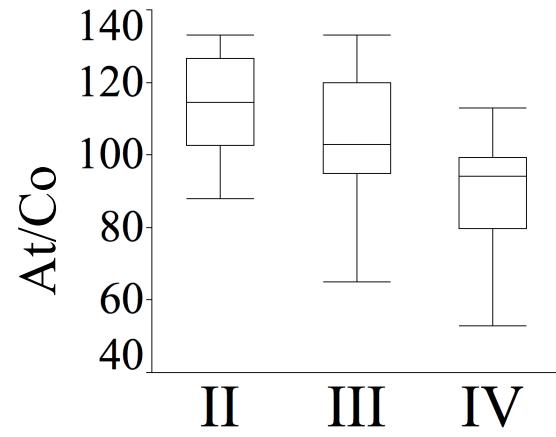
FIQ; Full-scale intelligence quotient

WMS-R; Wechsler Memory Scale Revised

Neuropsychological results calculated using Kruskal-Wallis test.

P; P value of between three groups

A**B****C****D****E**

A**B****C****D****E**