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Visuospatial memory improvement in patients with diffuse axonal injury (DAI): a 1-year follow-up study

Zaninotto AL, Vicentini JE, Solla DJF, Silva TT, Guirado VPM, Feltrin F, De Lucia MCS, Teixeira MJ, Paiva WS. Visuospatial memory improvement in patients with diffuse axonal injury (DAI): a 1-year follow-up study.

Objective: Diffuse axonal injury (DAI) is prevalent in traumatic brain injury (TBI), and is often associated with poor outcomes and cognitive impairment, including memory deficits. Few studies have explored visual memory after TBI and its relationship to executive functioning. Executive functioning is crucial for remembering an object's location, operating devices, driving, and route finding. We compared visual memory performance via the Rey–Osterrieth Complex Figure (ROCF) test 6 and 12 months after DAI.
Method: In total, 40 patients (mean age 28.7 years; 87.5% male) with moderate-to-severe DAI following a road traffic accident completed the 1-year follow-up. There was a three-phase prospective assessment. In phase 1 (1–3 months after trauma), patients completed the Beck Depression Inventory (BDI) and State-Trait Anxiety Inventory (STAI). In phases 2 (6 months) and 3 (12 months), they completed the BDI, STAI, and a neuropsychological battery [ROCF copy and recall, digit span forward/backward, Grooved Pegboard test, intelligence quotient (IQ) by Wechsler Adult Intelligence Scale-III (WAIS-III)].
Results: There was an improvement in ROCF recall over time ($p = 0.013$), but not ROCF copy ($p = 0.657$). There was no change in executive function (Savage scores) copy ($p = 0.230$) or recall ($p = 0.155$). Age, years of education, severity of the trauma, and IQ did not influence ROCF recall improvement.
Conclusion: There are time-dependent improvements in visual memory in patients with DAI. Neuroplasticity in the 1st months after trauma provides an opportunity for visuospatial memory learning. The present findings may be useful to formulate management plans for long-term TBI rehabilitation.

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Significant outcomes

- There exists a time-dependent natural improvement in visuospatial memory in patients with DAI.
- Neuroplasticity plays an important role in the natural course of DAI, particularly for visuospatial memory.

Limitations

- This was a single centre study and all inherent generalisation limitations apply.
- A lack of blinding of assessors could have resulted in bias.

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Introduction

Traumatic brain injury (TBI) is the leading cause of sequelae and death in children and young adults in western industrial countries (1,2), and is the worldwide leading external cause of death (3). TBI results in persistent dysfunction, which is primarily characterised by cognitive impairment (4). The most common type of TBI is diffuse axonal injury (DAI), the cause of which is angular or rotational acceleration and deceleration that stretches and shears brain axons, resulting in white matter damage (5–10). Unlike focal lesions, diffuse injury affects widespread cortical and subcortical neural networks, which compromises the brain's ability to compensate for damage. Both severe and moderate head injuries are associated with DAI (10), cognitive deficits (6), and poor clinical outcomes (7). Memory impairment is one of the most common residual deficits following TBI (8,11,12). The impairment is generally non-specific in patients, and can involve the encoding and retrieval of verbal and visual information equally, as DAI typically affects multiple brain networks (9).

A large number of studies have investigated the effects of TBI on verbal memory, which is to be expected given the relevance of verbal learning and memory in education, academic performance, and everyday functioning. However, few studies have explored visuospatial memory after brain injury (13,14). This ability is crucial for everyday activities such as remembering an object's location, operating devices, driving, and route finding. Many visuospatial tasks use familiar geometric signs, for which verbal bias may occur because such shapes can easily be encoded verbally. Thus, one of the most widely used instruments to evaluate visuospatial memory in clinical and experimental settings is the Rey–Osterrieth Complex Figure (ROCF) test (15,16). The ROCF test is particularly sensitive to diffuse damage after TBI (17), because the instrument is non-specific with respect to laterality (18). The complexity of the ROCF also demands executive function, requiring strategies and organisational approaches for drawing, and is sensitive to dysfunction of frontal–striatal systems (7,19).

Brooks (14) was one of the first to explore visual memory following TBI. He reported worse performance for a TBI group versus a control orthopaedic group. Scheid et al. (7) demonstrated worse performance in a group with TBI as compared with a healthy group in various cognitive domains, most notably in learning, and verbal and visuospatial memory. Thus, previous neuropsychological studies have shown the existence of visual memory impairment in those with TBI (14,19). Nevertheless, the samples were usually heterogeneous, which could have influenced the aetiology and severity of the TBI. Further, most of the study designs were cross-sectional. Accordingly, longitudinal examination of visuospatial memory performance in patients with DAI has been little explored. Our primary aim was to detect cognitive changes in visuospatial memory between 6 and 12 months after TBI. Our secondary aim was to assess the role of executive function in visuospatial memory. We also carried out an exploratory analysis to verify the influence of potential confounding variables, namely age, intelligence quotient (IQ), years of education, and severity of the trauma. Our first hypothesis was that visuospatial memory would improve over time. Our second hypothesis was that visuospatial memory would depend on executive function, as the latter plays a role in memory processing. To test these hypotheses, we compared ROCF performance at 6 and 12 months after the trauma in a group of patients with moderate and severe TBI, who were diagnosed with DAI.

Method

This was a 1-year prospective one-arm longitudinal study with three levels of a repeated-measures independent variable. The project was approved by the Institutional Ethics Committee for Research (CAPPESQ: Comissão de Ética para Análise de Projetos de Pesquisa) of the University of São Paulo (USP; project number 0097/11) and by the Special Ethics and Research Committee of the Division of Psychology of the USP Hospital (project number 18/2010).

Subjects

The group consisted of 40 patients with moderate-to-severe traumatic DAI. The severity of DAI was defined using the Glasgow Coma Scale (GCS) (19). Inclusion criteria consisted of the following: the participant had sustained a TBI up to 3 months before taking part in this study, had experienced loss of consciousness for at least 30 min as a consequence of TBI, was between 18 and 55 years of age, had at least 4 years of education, and a GCS score of <13 points. Exclusion criteria consisted of the following: patients who had suffered more than one TBI, who exhibited evidence of abnormalities other than DAI according to 3-Tesla magnetic resonance imaging (MRI; e.g. contusions, epidural haematoma, subdural haematoma), or who had been diagnosed with neurological conditions (e.g. epilepsy, stroke, tumour) or psychiatric conditions (e.g. bipolar disorder, major depression, or other conditions requiring admission to a psychiatric ward).

Setting

All data collection took place at the USP Clinics Hospital, Brazil. The sessions were structured using a fixed assessment battery to characterise depression and anxiety symptoms and cognitive measurements. The patients were recruited during the first follow-up medical visit after the trauma. They were invited to participate and received details of the study as explained in the consent form. As soon as they agreed to enrol in the project, we began phase 1 (see below). The follow-up assessments were scheduled during the same day the patient had his or her regular medical follow-up.

Instruments

Beck Depression Inventory (BDI) (20), Brazilian version (21). The BDI is a 21-question tool that measures symptoms of depression (e.g. sadness, pessimism, failure, guilt, suicidal ideation) using an ordinal response scale.

State scale from State-Trait Anxiety Inventory (STAI-S) (22), Brazilian version (23). The STAI-S consists of 20 questions that assess how patients feel at the moment, or felt in recent past, or what they anticipate their feelings would be in a specific situation that could happen in the future, or in a hypothetical situation.

ROCF test (15,16,24,25). In the ROCF test, the respondent first copies a complex geometric figure, which is shown on a stimulus card. Subsequently, after three minutes, he or she draws the figure again, from memory (ROCF recall). These tasks assess visuoconstruction and visual episodic memory, respectively. In addition to the traditional method of scoring the ROCF, we also used the *Savage scoring system* (26). This is a 0–6-point organisational scoring system that allows fast and accurate assessment of planning and organisation.

In the *Savage scoring system* (26), the ROCF is subdivided into five elements: the large rectangle, the diagonal cross, the vertical midline, the horizontal midline, and the vertex of the triangle on the right. Patients receive scores for reproducing each element as an unfragmented unit. Reproduction of the larger rectangle garners from 0 to 2 points to reflect its importance to the structure of the figure as a whole. All other elements are assigned 0 to 1 points, resulting in a range of scores from 0 to 6. The precision and accuracy of the drawing is not considered in this score. An organisational element receives a score when it is an unfragmented unit: (a) each side comprises a unit (e.g. each of the four sides of the rectangle) if drawn as a continuous line without interruption; and (b) all sides of the unit are drawn consecutively. The order in which the lines are drawn is unimportant, as long as they are drawn one after another. The patients do not receive points for organisation if part of the organisational unit is missing.

Digit span forward/backward from the Wechsler Adult Intelligence Scale-III (WAIS-III) (27). The forward task is considered to assess attentional verbal span capacity and the backward task assesses working memory. This test was applied in the 3 min between the end of the figure copy task and the start of figure recall task.

Grooved Pegboard Test (GPT) (28). GPT measures fine motor speed, visuomotor speed, and eye-hand coordination for the dominant hand (part A) and the non-dominant hand (part B). The test consists of 25 holes with randomly positioned slots. Pegs, which have a key along one side, must be rotated to match the hole before they can be inserted.

Intelligence quotient (IQ): vocabulary and matrix reasoning from WAIS-III (27). The Vocabulary subtest and Matrix Reasoning subtest of the WAIS-III are established methods for estimating general intelligence (IQ) (29,30). The subtests assess verbal knowledge and concept formation, and visuo-perceptual, abstraction, and visual reasoning abilities, respectively.

Procedure

All patients who completed the medical examination were submitted to 3-Tesla MRI and signed the consent form. Two experienced neuropsychologists performed the assessment, which had a maximum duration of 90 min and was completed during a single day. Patients were examined at three different points in time:

Phase 1. From 1 to 3 months after the injury. Patients completed the BDI and STAI-S and demographic questionnaires.

Phase 2. After 6 months of injury, the patients completed BDI and STAI-S questionnaires and received a cognitive assessment consisting of the ROCF, digit span forward and backward, GPT, and estimated IQ.

Phase 3. After 12 months of injury, the patients underwent the same procedure as in phase 2.

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The study endpoints followed the pattern of those used in clinical trials for TBI (31), in which cognitive functioning was assessed at 6 and 12 months post trauma (32–36).

Statistical analysis

Classical descriptive statistics were used according to the type and distribution of the data, which was assessed by graphical and statistical methods. For variables with a normal distribution, effects over time were compared using repeated-measures ANOVAs, whereas for data that were distributed non-normally, the Wilcoxon signed-rank test was used.

To assess the visuospatial memory improvement between 6 and 12 months after the TBI, the ROCF recall score percentage variation was considered the dependent variable in a multivariate linear regression model. Age, IQ, hand coordination, and severity of the trauma were included as independent variables. In addition, the analysis was adjusted for the baseline ROCF recall absolute score.

All tests were two-tailed and the significance level was set at 0.05. The analyses were performed using the Statistical Package for Social Sciences (SPSS) software version 20.0 for Windows (IBM SPSS statistics software, version 20; IBM Corp., Chicago, IL, USA).

Results

The sample consisted of 40 outpatients who were assessed prospectively for 1 year after the trauma. Table 1 provides basic demographic and clinical characteristics.

The majority of patients were young (28.7 ± 9.4 years), predominately male (35, 87.5%) and nearly all were victims of road traffic accidents (38, 95%). Their TBI was classified as severe in 60% (23) of cases and moderate in 40% (24). Mean IQ was 86.2 (± 8.5) as assessed at 6 months and 86.6 (± 7.7)

at 12 months. These values are ~1 SD below the normal average.

Mood symptoms, as measured by the BDI, did not differ among phases [$F(1. 49) = 0.731$, $p = 0.451$], with mean scores of 9.6 ± 7.8, 9.1 ± 7.0, and 7.5 ± 7.2 at phase 1, 2, and 3, respectively. Anxiety symptoms, assessed by the STAI-S, also showed no differences between phase 1 (40.5 ± 7.6), phase 2 (36.5 ± 9.5), and phase 3 (38.1 ± 9.0; $F(2) = 1.411$, $p = 0.254$).

Table 2 depicts the neuropsychological outcomes, comparing phase 2 with phase 3. IQ, attentional verbal span capacity, working memory, and executive functioning did not change over time. An improvement in non-dominant hand coordination, as measured by the GPT B, was detected [$t(34) = -2.677$, $p = 0.007$]. Visuospatial memory recall scores, as assessed by ROCF recall, improved from phase 2 to phase 3 [$t(38) = -2.611$, $p = 0.013$], but no differences were observed for ROCF copy (Fig. 1).

Table 3 shows the multivariate analysis results. Neither age, years of education, admission Glasgow Coma Scale (CGS), nor IQ influenced the ROCF recall improvement. The only significant variable was ROCF recall at 6 months. Each point of reduction in this score at 6 months predicted an improvement of 3.7% at 12 months ($\beta = -0.037$, 95% confidence interval (CI): -0.058 to -0.016, $p = 0.001$), which may, at least partly, reflect a regression to the mean phenomenon.

Discussion

Our follow-up study showed significant improvement in visuospatial memory as assessed by the ROCF test in DAI patients when comparing scores at 6 and 12 months after the trauma. This improvement appeared unaffected by executive function. There was a notable effect of time on visuospatial memory function. However, it is worth considering the

Table 1. Demographic information and clinical characteristics of diffuse axonal injury (DAI) patients

Variables	DAI patients ($n = 40$)
Age (years) – mean (SD)	28.7 (9.4)
Education (years) – mean (SD)	9.9 (2.8)
Male	35 (87.5)
Trauma severity	
Moderate	16 (40.0)
Severe	24 (60.0)
Trauma mechanism	
Motorcycle crash	22 (55.0)
Automotive crash	10 (25.0)
Running over	6 (15.0)
Others (fall and aggression)	2 (5.0)

Data are presented as n (%), unless otherwise stated.

Table 2. Neuropsychological outcomes of diffuse axonal injury patients ($n = 40$)

Variables	Phase 2: 6 months	Phase 3: 1 year	t or z value (df)	p-Value
IQ estimative	86.2 (8.5)	86.6 (7.7)	−0.325 (39)	0.747
Forward digit	6.4 (1.7)	6.6 (2.0)	−0.754 (39)	0.455
Backward digit	3.9 (1.4)	4.1 (1.4)	−0.894 (39)	0.377
ROCF copy	34.0 (31.5–35.0)	34.0 (31.0–36.0)	−0.113 (39)	0.657
ROCF recall	14.3 (8.0)	16.6 (7.1)	−2.611 (38)	0.013
Savage copy	4.5 (1.5)	4.7 (1.2)	−1.220 (37)	0.230
Savage recall	3.5 (1.9)	3.9 (2.0)	−1.453 (37)	0.155
GPT A	87.5 (73.5–102.5)	81.5 (73.5–93.0)	−1.269 (39)	0.204
GPT B	97.0 (85.0–112.0)	92.0 (80–115.0)	−2.677 (34)	0.007

GPT, Grooved Pegboard Test; IQ, intelligence quotient; ROCF, Rey–Osterrieth Complex Figure.

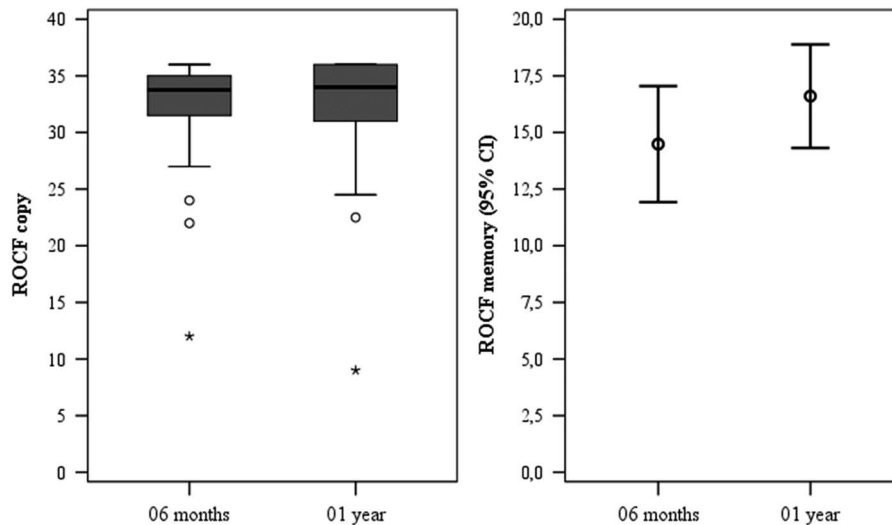Data are presented as mean (SD) or median (1st–3rd quartiles), as appropriate.

Fig. 1. Rey–Osterrieth Complex Figure (ROCF) copy and recall at 6 months and 1 year.

Table 3. Multivariate analysis for predictors of visual memory improvement (ROCF recall variation) in diffuse axonal injury patients ($n = 40$)

Variables	β	SE	Std. β	95% CI	p-Value
Age	−0.005	0.009	−0.087	−0.023–0.013	0.575
Education (years)	0.054	0.032	0.278	−0.011–0.118	0.100
Admission GCS	0.008	0.028	0.040	−0.049–0.064	0.785
IQ estimative	−0.013	0.011	−0.210	−0.035–0.008	0.219
ROCF recall at 6 months	−0.037	0.010	−0.535	−0.058–0.016	0.001

CI, confidence interval; GCS, Glasgow Coma Scale; IQ, intelligence quotient; ROCF, Rey–Osterrieth Complex Figure; Std., standardised.
Model summary: r^2 0.388, $F(5) = 4.056$, $p = 0.006$.

possible effect of regression to the mean, as the greater the loss of visuospatial memory after TBI (lower ROCF recall in the early phase), the greater the improvement towards (hypothetical) original levels. This phenomenon can be related to neuroplasticity in chronic changes after TBI. In patients with brain injury, neuroplasticity is a mechanism that compensates for neural damage and re-establishes function (37). In the chronic stage, axonal remyelination occurs accompanied by greater recovery.

There exists controversy regarding the most important period of cognitive recovery following TBI. Although 6–12 months post trauma has been proposed (38,39), others have suggested between 1 month and 1 year after the injury (40). Even following recovery, it is likely that patients do not return to their premorbid skill levels and some memory deficits can persist even after 10 years (7,41,42). Despite improved visuospatial memory performance, patients continue to generate worse scores than normative data for healthy subjects (25).

Nevertheless, when comparing months 6 and 12 after the trauma with baseline, only visuospatial memory and manual motor performance were significantly improved, suggesting a therapeutic window for selected domains. High educational levels and genetic predisposition are assumed to be involved in higher cognitive performance. Patients with greater cognitive reserve have a higher threshold for brain injury before clinical deficits appear and ultimately may suffer less impairment (43). Indeed, although IQ estimates tended to be associated with higher ROCF recall at 6 months, and years of education was associated with higher ROCF recall at 12 months (data not shown), neither predicted the improvements on this test between 6 and 12 months.

Regardless of the role of executive function in visuoconstruction ability and planning, our secondary analysis did not show any relationships between the Savage scoring system and improvement on the ROCF recall test. We used the Savage score to assess whether patients were able to make a structured reproduction of a figure during the copy and recall task. We hypothesised that the Savage scoring system would provide a simple way of measuring executive function, which is one of the most complex cognitive abilities in humans. An organised reproduction ability was expected to be associated with better memory recall. Thus, Savage scoring was used to assess the role of executive function on memory recall as measured by the ROCF.

Difficulties with fine motor coordination could have disrupted patients' performance. We measured such coordination via the GPT, to identify any potential bias in reproduction ability. Arm paresis may occur after TBI, but most patients show good recovery within the first 2 months (17). Furthermore, we found improved fine motor coordination over

time in the non-dominant hand, which would not lead to better drawing ability.

These results are of clinical relevance because visuospatial memory is independent of executive function, the former can be trained to increase performance even if the patient has a dysexecutive syndrome.

There is an association between TBI and an increased risk of developing depression and anxiety, which may lead to worse functional, social, and cognitive outcomes (44). In our study, anxiety and depression symptoms were at the minimum level during the three phases of the studies. It is possible that these low scores were responsible for the lack of association between anxiety and depression symptoms and the cognitive outcome measures. Similarly, a previous study found no association between visuospatial memory and depressive symptoms (12).

Our study has several limitations. Although we cannot discard the possibility that practice influenced the ROCF test scores, we believe this to be unlikely. No studies have reported ROCF test–retest learning and there is some evidence that the same memory tests can be used successfully in follow-up assessments (45,46). ROCF is considered a difficult image to learn in a clinical setting, and in the current study, the ROCF figure was presented twice to the same patient with 6 months between presentations. Moreover, visual deficits following moderate and severe TBI are common (47). These deficits are related to abnormal saccades, pursuit, convergence, accommodation (48), and perceptual organisation (49). In our previous study (49), we observed patients' difficulties in combining elements into a whole by means of elementary grouping processes, as assessed by the Leunen perceptual organisation screening test. We analysed visuospatial memory using the ROCF test and investigated whether the scores were related to executive function, as measured by the Savage scoring system. However, we found no such association.

No reports exist to date regarding sex differences in visuospatial memory, visual organisation, or visual perception in patients with TBI. Between 70% and 85% of patients with TBI are male (50,51), which was also true of our sample, thus supporting the internal and external validity of our results.

There exists the possibility of bias in the current study due to a lack of blinding. We tried to avoid bias by using standardised, objective tests to assess mood and cognition. Possible sampling bias should also be considered. The ratio of patients screened to those followed was large, that is, a small and perhaps distinctive group of patients with DAI was able to participate in the study.

Overall, our results suggest that patients with DAI have an open window for neuroplasticity of visuospatial memory between 6 and 12 months after the trauma. Clinicians need to be aware of this natural improvement in visuospatial memory, as interventions during this phase could take advantage of the increased neuroplasticity.

In conclusion, our findings suggest that the ROCF test is suitable for assessing visuospatial memory following TBI and that neural reorganisation appears time dependent. The natural course of DAI recovery due to neuroplasticity remains unknown. Understanding this natural recovery course would be helpful when identifying effective rehabilitation strategies.

Conflicts of Interest

The authors declare there are no conflicts of interest pertaining to this work.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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