Impaired visuospatial but not verbal working memory in adult patients with neurofibromatosis type 1

Hanlu Tang (✉ ttsw1994@163.com )
Beijing Tiantan Hospital  https://orcid.org/0000-0003-4766-6136

Qiong Wu
Beijing Key Laboratory of Learning and Cognition, School of Psychology, Capital Normal University, Beijing, China.

Shiwei Li
Beijing Tiantan Hospital

Yehong Fang
Beijing Tiantan Hospital

Zhijun Yang
Beijing Tiantan Hospital

Bo Wang
Beijing Tiantan Hospital

XingChao Wang
Beijing Tiantan Hospital

Pinan Liu
Beijing Tiantan Hospital

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Abstract

Purpose

Cognitive dysfunction is one of the main symptoms of neurofibromatosis type 1 (NF1). As an important advanced cognitive function, working memory (WM) has rarely been systematically analyzed in NF1 by isolating the particular domain of WM, and existing data involving WM in adults with NF1 are controversial. This study aimed to clarify the characteristics of WM in NF1 from the perspective of the adult population.

Methods

We comprehensively analyzed WM in both verbal and visuospatial WM domains by using the N-back task (including the verbal N-back task and the visuospatial N-back task) in 31 adults with NF1 and 34 healthy controls (HCs) matched for age, gender, education levels and general cognitive status. The accuracy and reaction times (RTs) in the N-back task were entered into repeated-measure ANOVAs.

Results

Compared with HCs, adults with NF1 presented significantly lower mean accuracy ($F_{(1,62)} = 4.60, p = 0.036$) and longer RTs ($F_{(1,62)} = 4.91, p = 0.03$) in the visuospatial N-back task, and the gap became more obvious as the difficulty levels increased. However, no significant difference was found in the verbal N-back task (accuracy: $F_{(1,62)} = 2.41, p = 0.13$; RTs: $F_{(1,62)} < 1$).

Conclusions

Our study found that adults with NF1 had selective deficits in WM (impaired visuospatial but not verbal WM), and visuospatial WM dysfunction became obvious as memory load increased. Our findings supplement and refine the existing data on WM in NF1 disorder and demonstrate functional independence between verbal and visuospatial WM.

Introduction

Neurofibromatosis type 1 (NF1) is an autosomal-dominant disorder with an average global prevalence of approximately 1/3000$^{[1]}$. The disease not only causes neurofibromas, café-au-lait macules, optic pathway gliomas and malignant peripheral nerve sheath tumors but also leads to structural changes in the brain$^{[1, 2]}$ as well as various cognitive dysfunctions$^{[3]}$. Compared with unaffected peers, individuals with NF1 usually exhibit deficits in many important cognitive domains, such as IQ$^{[4]}$, visual perception$^{[5]}$, language$^{[6]}$, reading$^{[3]}$, calculation$^{[7]}$, attention deficit$^{[8, 9]}$ and executive function$^{[10]}$. In addition, working
memory (WM), an important advanced cognitive function, has received increasing attention from clinicians.

WM is an important part of cognitive processing, providing temporary storage and manipulating essential information for complex cognitive activities such as learning, reasoning and language comprehension\cite{11, 12}. Based on the most influential model of WM provided by Baddeley et al\cite{13}, WM can be subdivided into verbal WM and visuospatial WM, involving the temporary maintenance and manipulation of verbal and visuospatial information, respectively\cite{14, 15}. Verbal WM supports language such as syntactic and semantic operations, as well as vocabulary acquisition during development\cite{16}, and visuospatial WM supports perception, attention, actions to guide thought and higher-level cognition\cite{17, 18}. Their deficits will have an important effect on education- and work-related activities and consequently affect the quality of life. Moreover, WM dysfunction is heritable and is associated with susceptibility to schizophrenia\cite{19}.

To date, previous NF1 studies involving WM have mainly focused on children\cite{20–22}, with few studies involving adult populations. Furthermore, the sample size of previous studies on WM involving adult patients was insufficient\cite{23, 24}, and one previous study recruited unmatched-IQ healthy controls (HCs)\cite{23}. The paucity and deficiency of WM data on adults with NF1 have limited our further understanding of NF1 disease from the perspective of the population characteristics. Moreover, most previous NF1 studies paid only one-sided attention to the general estimation of WM or focused on spatial WM\cite{20, 21}, verbal WM\cite{25, 26}, auditory WM\cite{24}, or phonological short-term WM\cite{27} separately. Few studies have conducted an integral analysis of WM in individuals with NF1 by isolating different domains of WM. Furthermore, previous methods measuring WM in NF1 varied without a uniform standard. It is debatable whether these methods can accurately assess WM. In addition, previous investigations have claimed that verbal and visuospatial WM have different domain-specific cortical networks in the human brain\cite{28–30}. However, few studies have offered evidence for this view.

To address the previous problems and biases, the current study recruited adults with NF1 and matched HCs to comprehensively analyze the features of WM in individuals with NF1 in both verbal and visuospatial WM domains based on Baddeley's WM model\cite{13} using the N-back task\cite{31}, which allows the verbal and visuospatial domains of WM to be precisely and simultaneously examined. The aims of our study were as follows: (1) to determine whether adults with NF1 exhibit deficits in WM (including verbal and visuospatial WM) and, if so, to clarify the detailed information of the deficits; (2) to supplement and refine the existing data on WM in NF1 disease to provide a theoretical basis for clinical drug therapy and psychological intervention; and (3) to provide behavioral evidence for the previous view that verbal and spatial WM are independent of each other functionally and anatomically.

**Materials And Methods**

**Participants**
We recruited thirty-three adult patients with NF1 from the Neurofibromatosis Outpatient Department of Beijing Tiantan Hospital between 2019 and 2020. Thirty-six HCs were recruited from the community. Two patients were excluded for not completing the task, and two healthy controls were excluded due to misunderstanding the introduction. The final sample included 31 adults with NF1 and 34 HCs. All individuals with NF1 fulfilled the diagnostic criteria established by the National Institutes of Health (NIH) Consensus Development Conference[32], and most of them had café-au-lait macules or small benign subcutaneous nodules on the body, but these skin lesions did not affect their daily activities. All patients were clinically stable, and none of them presented abnormalities on general neurological examination or limitations in daily life. Seven patients complained of mild memory decline, and three patients complained of attention deficits. All participants were right-handed and had normal or corrected-to-normal vision.

All participants were required to complete the short form of the Beck Depression Inventory (BDI-SF)[33] and the Mini-Mental State Examination (MMSE)[34]. The BDI-SF was used to quantify the general emotional state of the participants to avoid interference from emotional factors. Scores below or equal to 4 points indicate no or minimal depressive symptoms. Scores above this threshold indicate mild (5–7 points), moderate (8–15 points) or severe (≥16 points) depressive symptoms. The MMSE was used to assess the general cognitive status of the participants to ensure their ability to understand and cooperate in the further tasks of advanced cognitive function. Any score greater than or equal to 25 points (out of 30) indicates normal cognition. Scores below this threshold indicate mild (21–24 points), moderate (10–20 points) or severe (≤9 points) cognitive deficits.

The admission criteria of the individuals with NF1 and the HCs were (1) 18 ≤ age ≤ 60 y; (2) an MMSE score ≥ 24; (3) no severe NF1 symptoms, such as plexiform neurofibromas or malignant peripheral nerve sheath tumors; (4) no intracranial surgery history; (5) no history of serious chronic disease; (6) no mental illness or family history of mental illness; (7) no recent use of any medications that could affect cognitive abilities; and (8) voluntary participation as given by a signed consent document. All participants experienced the same experimental procedures in the same quiet room. All tests were administered by the same tester. This study was approved by the Medical Ethics Committee of Beijing Tiantan Hospital, Capital Medical University, China.

The final sample included 31 adults with NF1 (12 males and 19 females) and 34 HCs (10 males and 24 females). The ages of the individuals with NF1 and the HCs were 30.4 ± 7.7 and 31.1 ± 9.8 y, respectively. The years of education of the individuals with NF1 and the HCs were 12.8 ± 3.1 and 13.0 ± 3.3 y, respectively. No individuals with NF1 or HCs presented with cognitive deficits as measured by the MMSE (28.8 ± 1.2 and 29.2 ± 0.9, respectively). The BDI-SF scores of the individuals with NF1 indicated moderate depressive mood, and the BDI-SF scores of the HCs indicated no or minimal depressive mood (8.9 ± 7.5 and 2.6 ± 3.5, respectively). The individuals with NF1 and HCs were matched for age (t(63) = -0.33, p = 0.741), gender (χ²(63) = 0.63, p = 0.429), educational attainment (t(63) = -0.24, p = 0.810) and MMSE score
The BDI-SF score ($t'_{(63)} = 4.28, p = 0.000$) was not matched and was removed as a covariate in the data analysis (Table 1).

### Table 1
Demographic characteristics of participants

|                | Age (years) | Gender | Education (years) | MMSE     | BDI-SF    |
|----------------|-------------|--------|-------------------|----------|-----------|
| **Mean (95% CI)** | Mean (95% CI) | Mean (95% CI) | Mean (95% CI) | Mean (95% CI) |
| NF1             | 30.4 (2.8)  | 12 males | 12.8 (1.1)        | 28.8 (0.4) | 8.9 (2.7) |
| HCs             | 31.1 (3.4)  | 10 males | 13.0 (1.2)        | 29.2 (0.3) | 2.6 (1.2) |
| $p$ value       | 0.741       | 0.429   | 0.810             | 0.105    | 0.000     |

Age: the age at the testing date; BDI: the short form of the Beck Depression Inventory, a measure of baseline mood; CI: confidence interval; HCs: healthy controls; MMSE: Mini-Mental Status Examination, a test for cognitive impairment; NF1: patients with neurofibromatosis type 1.

### The N-back Task

The N-back task was used to measure the participants’ accuracy and reaction times (RTs) to the stimulus under various memory load levels, including the visuospatial N-back task and the verbal N-back task, which examined the abilities of visuospatial WM and verbal WM, respectively. The participants were required to determine whether the presented stimulus was the same as the Nth stimulus before. The N-back program runs on the E-prime™ (Psychology Software Tools, Pittsburgh, PA, USA).

In the visuospatial N-back task, four gray boxes (up, down, left, right) were located in the center of the screen (Fig. 1a). In each trial, a random box turned yellowed for 500 ms followed by an interstimulus interval of 1000 ms. There were three conditions: 0-back, 1-back, and 2-back. The participants were instructed to indicate the location of the previous Nth box that turned yellow using the left, right, up, and down direction keys. In the 0-back condition, the participants pressed the corresponding key as the box turned yellow. The participants’ RTs and accuracy were recorded. The task consisted of 18 blocks with six blocks in each condition and was presented in random order. Each block contained 20 trials and lasted approximately 30 s. The total time of the visuospatial N-back task was approximately 9 minutes. The participants practiced the task for 3 blocks (0-back, 1-back, 2-back each) before the formal test began.

In the verbal N-back task, a series of letters were presented one by one for 500 ms, followed by a 3500 ms blank screen (Fig. 1b). The four blocks (0-back, 1-back, 2-back, 3-back) were presented once in a fixed order, with 18 letters in each block. In each trial, the participants were asked to press the left button if the current letter was the same as the Nth letter before; otherwise, they pressed the right button. For the 0-back condition, the participants were required to indicate whether the current letter was “X”. The participants’ accuracy and RTs were recorded. The total time for the verbal N-back task was approximately 5 minutes.
Data analysis

The data from visuospatial and verbal N-back tasks were analyzed separately because there were different levels of N in each task. The accuracy and RTs were entered into repeated-measure ANOVAs, with the task difficulty level (3 for the visuospatial N-back task and 4 for the verbal N-back task) as the within-subject factor and the group (NF1 and HCs) as the between-subject factor. Since the individuals with NF1 showed a slightly depressed mood, as indicated by higher BDI-SF scores than those of the HCs, we controlled this potential confounding factor by regressing out the BDI scores as the covariate.

Results

In the visuospatial N-back task, the overall mean accuracies of the NF1 and HCs groups were 62.84% ± 12.67% and 72.94% ± 13.41%, respectively, and their RTs were 598 ± 145 ms and 491 ± 158 ms, respectively (see Table 2 for details). The repeated-measure ANOVA for accuracy showed a significant main effect of task difficulty level \( F_{(2,124)} = 119.91, p < 0.001 \); Fig. 2a), with less accurate responses as the difficulty levels increased. Importantly, we found a significant main effect of group \( F_{(1,62)} = 4.60, p = 0.036 \). Patients with NF1 showed lower performance accuracy than HCs, indicating a significant impairment in visuospatial WM. There was no interaction between group and task difficulty \( F_{(2,124)} = 2.16, p = 0.12 \). The repeated-measure ANOVA for RTs revealed similar results (task difficulty main effect: \( F_{(2,124)} = 3.85, p = 0.024 \); group main effect: \( F_{(1,62)} = 4.91, p = 0.03 \); Fig. 2b). Patients with NF1 were slower than the HCs, which was mainly caused by difficult levels of the task (i.e., 1-back and 2-back), as evidenced by a significant interaction effect on RTs \( F_{(2,124)} = 6.50, p = 0.002 \).
### Table 2
The details of the N-back task

|                  | NF1                        | HCs                        |
|------------------|----------------------------|----------------------------|
|                  | Accuracy (%)   | RTs (ms) | Accuracy (%)   | RTs (ms) |
|                  | Mean          | SD      | Mean          | SD      | Mean          | SD      | Mean          | SD      |
| **Visuospatial N-back Task** |           |           |               |           |               |           |               |           |
| 0-back           | 97.34%        | 3.65%    | 494           | 115      | 98.65%        | 2.06%    | 493           | 90      |
| 1-back           | 60.04%        | 26.46%   | 679           | 246      | 72.66%        | 20.34%   | 493           | 237     |
| 2-back           | 31.16%        | 14.29%   | 620           | 156      | 47.52%        | 22.64%   | 487           | 202     |
| **Verbal N-back Task** |           |           |               |           |               |           |               |           |
| 0-back           | 94.62%        | 5.46%    | 591           | 120      | 96.73%        | 4.95%    | 610           | 128     |
| 1-back           | 91.46%        | 10.06%   | 728           | 180      | 96.19%        | 5.95%    | 710           | 183     |
| 2-back           | 84.07%        | 14.33%   | 802           | 157      | 90.80%        | 9.13%    | 877           | 255     |
| 3-back           | 78.49%        | 16.12%   | 890           | 268      | 84.90%        | 11.41%   | 976           | 321     |

HCs: health controls; NF1: patients with neurofibromatosis type 1; RTs: reaction times; SD: standard deviation.

In the verbal N-back task, the overall mean accuracies of the NF1 and HCs groups were 87.16% ± 8.31% and 92.16% ± 4.71%, respectively, and their RTs were 753 ± 157 ms and 793 ± 193 ms, respectively (see Table 2 for details). The repeated-measure ANOVAs for accuracy and RTs both revealed significant main effects of task difficulty level (accuracy: $F_{(3,186)} = 10.94, p<0.001$; RTs: $F_{(3,186)} = 46.63, p<0.001$; Fig. 3a and 3b), with less accurate and slower responses as the difficulty levels increased. Interestingly, we did not find a significant main effect of group (accuracy: $F_{(1,62)} = 2.41, p = 0.13$; RTs: $F_{(1,62)} < 1$) or its interaction with task difficulty for either accuracy or RTs (accuracy: $F_{(3,186)} < 1$; RTs: $F_{(3,186)} = 1.01, p = 0.36$), indicating an intact verbal WM ability in the participants with NF1.

Together, the results from the visuospatial and verbal N-back tasks suggest that the participants with NF1 have selective deficits in visuospatial WM but intact capability in verbal WM.

**Discussion**

In the current study, we analyzed WM in 31 adults with NF1 and 34 HCs by using the N-back task, and the results showed that adults with NF1 presented selective deficits in different subgroups of WM.

**Visuospatial WM deficits in adult patients with NF1**
In the visuospatial N-back task, the results showed that the accuracy decreased as task difficulty levels increased in both NF1 patients and HCs. The mean accuracy of NF1 was significantly lower than that of HCs. In the 0-back task, adults with NF1 performed no difference from HCs. However, as the task difficulty levels increased, the gap between the NF1 patients and HCs gradually became more obvious, especially in the 2-back task. The result of RTs revealed a similar phenomenon. These results suggest that adults with NF1 have significant deficits in visuospatial WM compared with HCs, and the deficits became more obvious as memory load increased. Our finding was consistent with the results of the Huijbregts S et al\cite{36} study, in which WM deficits became apparent in children with NF1 as task difficulty increased.

A visuospatial WM deficit was also reported in children and adolescents with NF1 (see S1), which suggested that this deficit could occur early in the life of individuals with NF1 and affect the development and academic achievement of school-age patients. Although a study recruiting 5 elderly individuals with NF1 (age>60, mean age 65) found that elderly NF1 patients presented spatial WM impairments compared with HCs\cite{26}, few previous studies noticed visuospatial WM deficits in adult populations. Shilyansky C. et al\cite{23} assessed spatial WM in adults with NF1 via two spatial delayed response tasks, and adults with NF1 presented significantly lower accuracy than HCs, with an apparent decline as memory load increased. However, his study used non-IQ-matched HCs for comparisons. In our study, we demonstrated visuospatial WM deficits in NF1 adults compared to HCs without general cognitive status bias by using the MMSE. In addition, combined with our reviewed previous literature involving WM in individuals with NF1 (see S1), we found visuospatial WM dysfunction to be a typical feature of NF1 patients across the lifespan (from childhood to advanced adulthood). Therefore, we should pay more attention to WM dysfunction in individuals with NF1 in the clinic.

**No verbal WM deficits in adult patients with NF1**

The present study showed no difference in verbal WM between adults with NF1 and HCs, which supported two previous studies on children patients. Hyman et al\cite{25} found that there was no noticeable difference between NF1 patients and HCs in verbal WM, as assessed by both the digit span backwards test and the digit span forward minus digit span backwards test. Chaix Y et al\cite{27} reported no auditory-verbal WM or phonological short-term WM impairment in children with NF1 via the ”WM index” of the Wechsler Intelligence Scale for Children–Fourth Edition and the pseudoword repetition task, respectively. The descriptions and definitions of verbal WM in previous studies varied, lacking universal terminology. Different researchers define verbal WM differently based on their educational background and professional affiliation, which makes it difficult for us to interpret and compare the results of these studies.

However, several previous studies put forward different opinions. Descheemaeker M J et al\cite{24} reported auditory WM deficits in adults with NF1 through the auditory verbal learning test (Dutch version). Costa Dde S et al\cite{26} found that elderly individuals with NF1 presented verbal WM impairments compared with HCs through the digit span backwards and digit span forward tests. A possible reason for these conflicting results may be that the methods (such as batteries) used to assess verbal WM varied (see S1).
For example, previous studies have assessed verbal WM via the "WM index" of the Wechsler Adult Intelligence Scale, which is biased toward a composite score and can obscure or skew the measurement of verbal WM. In addition, several previous studies have assessed verbal WM via the digit span forward and backward test, which essentially measures attention and the executive component of WM, respectively\[^{37}\]. Therefore, the appropriateness of these measures is debatable. In the current study, we used the N-back task, which can better examine verbal and visuospatial WM, with the advantage of manipulating memory load by controlling the number of stimuli between the current stimulus and the target stimulus to increase memory load while eliminating other interfering factors\[^{35}\]. Moreover, most previous studies used non-IQ-matched HCs and did not consider the effects of depressive symptoms on WM\[^{38, 39}\]. These factors affect the accuracy of the research results and cause controversy. In our study, we used general cognitive status-controlled HCs and eliminated the effect of depressive symptoms as a covariate.

**Functional-neuroanatomical dissociation between verbal and visuospatial WM in NF1**

Jonides J et al\[^{28}\] found that verbal and visuospatial WM were implemented by different neural structures via positron emission tomography studies. Then, with the application of functional MRI, Gruber O et al\[^{30}\] further demonstrated that verbal and spatial WM were mediated by distinct neural networks with some overlapping and some distinct neural circuitry. The present study showed that adults with NF1 presented deficits in visuospatial WM but not verbal WM, which demonstrates that verbal and visuospatial WM exhibit functional dissociation. Our results offer new behavioral evidence for this established view. Dissociation has also been found in patients with autism\[^{40}\]. Moreover, dissociation could account for why individuals with NF1 complain of no difficulties in daily life but perform poorer than their peers in academic or advanced brain function activities because visuospatial WM involves higher cognitive functions than verbal WM.

**Potential neural mechanisms underlying WM dysfunction in NF1**

As a monogenic disease, NF1 provides a unique genetic model to explore and mechanistically dissect the molecular mechanism underlying WM. NF1 gene mutation is the core cause of WM impairment in NF1 patients. Reduced NF1 gene expression in neurons leads to decreased neurofibromin production, resulting in downstream molecular and signaling pathway abnormalities related to memory, such as reduced cAMP levels\[^{41, 42}\], increased GABA release\[^{23}\] and reduced long-term potentiation\[^{41}\]. Moreover, decreased neurofibromin production will cause low intracranial DA levels in individuals with NF1\[^{41}\], which is associated with WM impairments\[^{43}\]. Notably, prefrontal DA levels are related to the activity of catechol-O-
methyltransferase (COMT), which can degrade cortical DA levels\textsuperscript{[44]}. However, a variant of the \textit{COMT} gene (\textit{Val}→\textit{Met}) has reduced COMT activity, leading to higher prefrontal DA levels, which will ameliorate verbal WM deficits\textsuperscript{[45, 46]}. Individuals with \textit{Val/Val} genotypes, \textit{Val/Met} genotypes, and \textit{Met/Met} genotypes had lower, moderate, and higher performance in the N-back task, respectively\textsuperscript{[19]}. \textit{COMT} polymorphisms (\textit{Val/Val, Val/Met, Met/Met}) may account for the inconsistent results of previous studies involving verbal WM in individuals with NF1.

Additionally, the hypoactivation of key components of WM circuitry (the right parietal cortex and the left dorsolateral prefrontal cortex) and aberrant functional connectivity in individuals with NF1 may underlie their visuospatial WM difficulties\textsuperscript{[47]}. Furthermore, individuals with NF1 show a more diffuse pattern of increased brain activation than HCs during high- vs low-memory-load tasks, which may reflect a less efficient pattern of brain activity\textsuperscript{[47]}. This could explain why, in our study, the participants with NF1 performed worse than HCs during high-visuospatial-memory-load tasks (1-back and 2-back tasks) but not during low-memory-load tasks (0-back task). Further investigations of the neural mechanisms underlying WM dysfunction in NF1 will be conducted in the future.

**Conclusion**

Compared with HCs, adults with NF1 have selective deficits in WM (impaired visuospatial but not verbal WM), and visuospatial WM dysfunction becomes more obvious as memory load increases. Visuospatial WM dysfunction is a typical feature of NF1 across the lifespan (from childhood to advanced adulthood). Decreased NF1 gene expression and its downstream molecular and signaling pathway abnormalities as well as local brain neuronal activity abnormalities may be the potential neural mechanisms underlying WM dysfunction in NF1. Our results supplement and refine WM data in NF1 and demonstrate functional separation between visuospatial and verbal WM.

**Declarations**

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**Conflicts of interest** All authors report no conflict of interest in this study.

**Code availability** Not applicable

**Authors’ contributions** PL, XW, and QW designed the study. Data collection was performed by QW, HT, and SL. HT and QW performed data-analysis and wrote the first and successive versions of the manuscript. All authors contributed to the interpretation of the results, intellectual content, critical revisions to the
drafts of the paper, and approved the final version. XW and PL had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**Ethics approval** This study was approved by the Medical Ethics Committee of Beijing Tiantan Hospital, Capital Medical University, China.

**Consent to participate** All participants provided informed consent before study procedures.

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Figures

Figure 1

Illustration of the 2-back condition of the visuospatial and verbal N-back tasks, respectively. (a) In the visuospatial N-back task, participants were instructed to indicate the location of the previous Nth (1- and 2-back) box that turned yellow using the direction keys of left, right, up, and down. For the 0-back condition, participants pressed the corresponding key as the box turned yellow. (b) In the verbal N-back task, participants pressed the left button if the current letter was the same as the Nth (1-, 2- and 3-back) letter before, otherwise pressed the right button. For the 0-back condition, participants were required to indicate whether the current letter was “X”.

Figure 2
Results on accuracy (a) and reaction times (b) in the visuospatial N-back task. Adult NF1 patients showed deficits in visuospatial WM compared with HCs. Error bar was 95% confidence interval. HCs, healthy controls; NF1, adults with neurofibromatosis type 1.

Figure 3

Results on accuracy (a) and reaction times (b) in the verbal N-back task. Adult NF1 patients showed no deficits in verbal WM compared with HCs. Error bar was 95% confidence interval. HCs, healthy controls; NF1, adults with neurofibromatosis type 1.

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