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Visual–spatial and visuomotor functioning in adults with neurofibromatosis type 1

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Abstract

Background Neurofibromatosis type 1 (NF1) is a neurodevelopmental genetic disorder associated with visual–spatial and visuomotor deficits, which have not been studied well in adults with NF1.
Methods In 22 adults with NF1 and 31 controls, visuomotor functioning was assessed by measuring eye latency, hand latency and hand accuracy during visuomotor tasks. Visual–spatial functioning was assessed by measuring eye movement responses during the Visual Threshold Task.
Results The NF1 group had a significantly shorter eye latency than the control group and was less accurate in their hand movements during specific visuomotor tasks. The groups showed no differences in eye movement responses during the Visual Threshold Task and in hand latency during the visuomotor tasks.
Conclusions In contrast to studies in children with NF1, we found no alterations in visual–spatial information processing in adults. Impairments in eye latency and hand accuracy during specific visuomotor tasks may indicate deficits in visuomotor functioning in adults with NF1.

Keywords adult, eye-tracking, neurofibromatosis type 1, visual–motor

Background

Neurofibromatosis type 1 (NF1) is a neurodevelopmental genetic disorder associated with various somatic symptoms and cognitive disabilities (Ferner 2007). Cognition can refer to learning, but also the development of cognitive abilities including perception and motor skills (Lai *et al.* 2013). Cognitive disabilities in NF1 include deficits in attention, lower-than-average intelligence quotient, motor problems and visual–spatial deficits (Hyman *et al.* 2005; Krab *et al.* 2011; Van der Vaart *et al.* 2016; Rietman *et al.* 2017; Ottenhoff *et al.* 2020). The visual–spatial and motor deficits have been extensively studied in children with NF1 using neuropsychological tasks, but limited studies have been performed in adults with NF1. Adults with NF1 experience several problems in performing daily cognitive activities, which affect their quality of life; these problems may in part be caused by deficits in the integration of the visual and motor system

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(Crawford *et al.* 2015; Gutmann *et al.* 2017; Varni *et al.* 2019).

The visual–spatial function includes cognitive processes to identify a visual stimulus, its location and visual and spatial relationships between objects. In the human brain, the parietal–occipital region processes visual–spatial information (Grafton *et al.* 1992; Kattah & Freehill 1993; Galati *et al.* 2011). Impairment in visual–spatial function has been shown in children and adults with NF1 using paper-based neuropsychological tests including the judgement of line orientation and Rey complex figure test (Levine *et al.* 2006; Van der Vaart *et al.* 2016). The performance on the Rey complex figure test showed the largest deficits in children with NF1 in a study that evaluated cognitive outcome measures in clinical trials (Van der Vaart *et al.* 2016). Deficits in visual–spatial function have been reported in adults with NF1 on the same tests (Zoller *et al.* 1997; Uttner *et al.* 2003; Pavol *et al.* 2006; Descheemaeker *et al.* 2013). The visual information process could be measured by making use of an electroencephalography (EEG) set-up to measure visual evoked potentials (VEPs). Previous studies observed abnormal VEPs in 26–51% of people with NF1 (Jabbari *et al.* 1985; Iannaccone *et al.* 2002; Ammendola *et al.* 2006; Yerdelen *et al.* 2011; Nebbioso *et al.* 2020). Furthermore, a common feature of NF1 is the presence of optic nerve gliomas, which have an effect on visual function.

Visual–spatial information is processed and translated to the visuomotor network to perform eye and hand movements (Corbetta *et al.* 2008). The human visuomotor network involves the sensory, attentional, executive and motor systems (Coiner *et al.* 2019). Visuomotor performance can be affected by disruption of the integration of these different domains in the brain. The visuomotor network plays an important role in the daily effortful cognitive activities. Moreover, children and adults with NF1 have shown disabilities in motor learning (Krab *et al.* 2011; Zimerman *et al.* 2015), fine motor skills (Johnson *et al.* 2010; Rietman *et al.* 2017) and voluntary muscle force (Souza *et al.* 2009). Additionally, adults with NF1 were slower in their hand movements in a motor skill learning task (Castricum, Tulen, Taal, *et al.* 2022). Therefore, adults with NF1 may suffer from deficits in the integration of the visual and motor system.

Visual–spatial and visuomotor deficits in adults with NF1 have hitherto been assessed by a diversity of paper-based neuropsychological tests. Eye and hand movement responses are related to the activity of the nervous system and could indicate deficits in the underlying neurophysiology of cognitive deficits in NF1 (Tinga *et al.* 2019). Interestingly, Sailer *et al.* (2005) showed that eye and hand movement responses changed while learning a new visuomotor task. Visual–spatial and visuomotor functioning can be quantitatively assessed by measuring eye and hand movement responses based on eye-tracking tasks (Pel *et al.* 2010; de Boer *et al.* 2015; Kooiker *et al.* 2016). These measures have several advantages over the more conventional paper-based assessments. First, the measures can objectively assess the underlying neurophysiology of the visual and motor system. Secondly, the measures are easy to perform and limited task instructions are needed. Furthermore, the measures can be collected in a short time duration of 5 to 20 min. Lastly, it has been shown that participants are often unaware of their visual behaviour including eye movement responses (Kok *et al.* 2017).

Visual–spatial function can be assessed with a Visual Threshold Task showing different conditions of varying difficulty of detection (Kooiker *et al.* 2016). During this task, the reaction time to fixation and fixation duration of the eye movement response can be measured (Kooiker *et al.* 2016). Visuomotor function is often assessed with multiple repetitive eye–hand coordination tasks (Mosimann *et al.* 2005). Eye–hand coordination tasks can include the Trajectory Prediction Task and various Tapping Tasks (Verheij *et al.* 2012; Muilwijk *et al.* 2013). During these tasks, the eye latency, and hand latency and hand accuracy could indicate deficits in the integration of the visual and motor system. In studies of cognitive processes, the commonly used time-dependent eye movement responses provide information related to cognitive processes related to learning (Lai *et al.* 2013).

Previous studies showed that eye movement responses were altered in various disorders with a neurodevelopmental basis, including autism, attention-deficit/hyperactivity disorder (ADHD) and schizophrenia (Sweeney *et al.* 2004; Itti 2015). Moreover, Tseng *et al.* (2013) showed distinctive features of eye movement responses of various disorders for potential use as a behavioural biomarker. Additionally, deficits in eye and hand movement

responses were observed in disorders as Parkinson's disease, Parkinson's disease dementia and Alzheimer's disease (Mosimann *et al.* 2005; Tippett & Sergio 2006; Verheij *et al.* 2012; Muilwijk *et al.* 2013; Gorges *et al.* 2014; Molitor *et al.* 2015). These studies showed that measuring eye and hand movement responses could indicate deficits in disorders associated with cognitive disabilities. Because eye and hand movement responses have a strong bidirectional relation, it is important to measure both to assess visuomotor integration (Gowen & Miall 2006).

We considered measures of eye and hand movement responses as potential neurophysiological outcome measures for adults with NF1. To our knowledge, eye and hand movement responses have not yet been assessed in adults with NF1. The study aims to quantitatively assess visual–spatial and visuomotor functioning in adults with NF1 measuring eye and hand movement responses. Based on previous studies, we expect alterations in the eye and hand movement responses during the visual–spatial assessments (i.e. the Visual Threshold Task) and the visuomotor assessments (i.e. the Trajectory Prediction Task and Tapping Tasks) in adults with NF1 compared to controls.

Methods

Subjects

This study enrolled 22 adults with NF1 and 31 controls between 18 and 55 years old. According to the inclusion and exclusion criteria, all subjects had no visual problems and used no psychoactive medication at the time of the study. All subjects had no neurological, psychiatric disorders (except intellectual disability), medical disorders or ocular pathology. Adults with NF1 had no optic nerve gliomas, or neurological disorders other than NF1. Adults with NF1 had a genetic or clinical diagnosis of NF1 and were outpatients from the ENCORE NF1 expertise centre for neurodevelopmental disorders at the Erasmus Medical Center Rotterdam. Controls were unaffected unrelated peers of the adults with NF1 or were recruited via online advertisements. The Dutch Central Medical Ethics Committee of the Erasmus Medical Center Rotterdam approved the study following the Declaration of Helsinki (2013). All subjects gave their written informed consent.

Procedures

The measures were executed in the afternoon between 12 PM and 5 PM at the Erasmus University Medical Center in Rotterdam. We measured the eye and hand movement responses using a keyboard in combination with a touch screen. Subjects were seated in front of the touch screen at a distance of arm's length. The Tobii Pro X3-120 Eye Tracker (Tobii Technology, Sweden) with infrared cornea reflection and pupil tracking was connected below the screen on the monitor. The Tobi system recorded the eye movements at a sampling rate of 120 Hz. Eye movements were recorded with Tobii Studio software after automatic correction of head movements. Before every task, a standardised calibration procedure was performed to verify a clear vision of the targets. The touch screen automatically recorded each touch or release from the hand by using a custom-made MATLAB script (MATLAB R2019b, MathWorks). Subjects performed several tasks in a fixed order taking a total duration of ~20 min (see also experimental procedures; Fig. 1). Participants practised the visuomotor tasks at least two times directly before the task. Additionally, prior to the eye-tracking procedure, we measured the level of sleepiness using the Karolinska sleepiness scale (KSS), a self-report questionnaire on a 9-point Likert scale (Akerstedt & Gillberg 1990), and we scored the level of education following the international standard classification of education (Schneider 2013).

Experimental procedures

The following tasks were presented in a fixed order (Fig. 1). The tasks were in order of degree of cognitive complexity of the tasks.

The Visual Threshold Task

The Visual Threshold Task assessed visual–spatial functioning and measured gaze responses (Kooiker *et al.* 2016). On each trial, a stimulus image was presented for 4 s. The stimulus was divided into four screen quadrants, and the image properties of one of the quadrants were different from the rest. Participants were instructed to look at the screen, but no explicit instructions were given about what to look for in the stimuli. We measured the reaction time to fixation and the target fixation duration. We defined

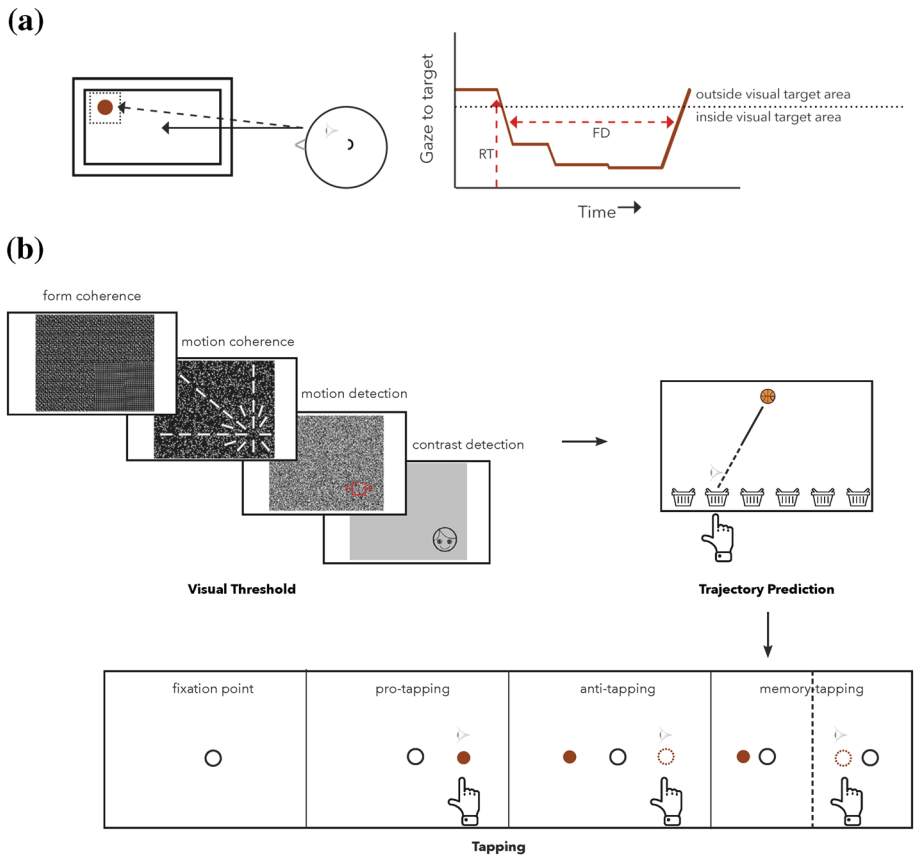

Figure 1. Schematic overview of the experimental procedures. (a) Left: Subjects were seated in front of the touch screen at a distance of arm's length. Visual stimuli were shown for 4 s in each of the four quadrants. The target area was a circular area with a radius of 6° in one of the four quadrants. Right: Visualisation of reaction time to fixation and fixation duration. Fixation duration is measured by the average duration of fixation on the target. An eye movement trace is represented in degrees from the target area (visual stimulus). The horizontal dashed line is the border of the visual stimulus. (b) The visual threshold, trajectory prediction and eye–hand coordination tasks. The order is indicated with arrows. The Visual Threshold Task consisted of various tasks including motion coherence, form coherence, motion detection and contrast detection. The visual stimuli were presented with varying difficulty of detection. During the Trajectory Prediction Task, a ball was shown in the top centre of the monitor in x = 0° from centre and y = 9.8° from centre prior to the start of a trial. The ball fell in the direction of one of the baskets with two different speeds: 75°/s and 150°/s. The ball disappeared halfway along the trajectory in 200 or 100 ms, respectively. The speeds were equally divided over the trials and baskets. Subjects had to predict in which basket the ball would have fallen. The Tapping Tasks include a pro-tapping, anti-tapping and memory-tapping task. Participants had to start by fixating on the black circle in the middle of the screen and tap on the red dot that appeared on the screen (pro-tapping), or on the opposite side of the screen where the red dot appeared (anti-tapping), or memorise the position of the red dot (memory-tapping) and tap on the screen where the red dot had appeared. The position of the peripheral circle was randomised. RT, reaction time; FD, fixation duration.

the target area as a circular region with a radius of 6°. The reaction time to fixation is the time of the visual process of a visual stimulus and the eye movement towards the visual target (Pel *et al.* 2010). The eye movement was the time between the start of a visual stimulus and the gaze entering the target area. Reaction time to fixation consisted of the fastest processing time of a visual stimulus and eye movement response. The target fixation duration was taken as the total time a participant's gaze was within the target area.

The Visual Threshold Task consisted of four subtasks: form coherence, motion coherence, motion detection and contrast detection, as previously described (Kooiker *et al.* 2016). Across these subtasks, the properties of the visual stimuli were varied

to vary the difficulty of detection. Across trials, we varied the form coherence of the target stimulus (100–50%), and motion coherence of the dots (100–60%) in decrements of 10%, and the contrast levels of the Hiding Heidi pictures (100%, 25%, 10%, 2.5% and 1.25%; adapted from Hyvärinen 1995). For example, in the 90% form coherence condition, 90% of the lines in the target quadrant followed the circular pattern, whereas the remaining 10% were randomly oriented. Throughout the Visual Threshold Task, the sub-tasks and conditions were presented in random order, such that each target was shown in each quadrant at least once. The task consisted of four trials per each condition.

The Trajectory Prediction Task

In the Trajectory Prediction Task (Serra *et al.* 2021), a ball (size: 2° visual angle) was shown in the top centre in x = 0° and y = 9.8° from centre prior. The ball fell in the direction of one of the baskets with different speeds: 75°/s and 150°/s. The ball disappeared halfway along the trajectory in 200 or 100 ms, respectively. The speeds were equally divided over the trials and baskets. Participants had to tap the correct basket as fast and accurately as possible. Participants perform reflexive eye movement responses to the position of the disappeared ball and a decisive eye movement to the basket of their choice, which is called the decisive eye latency. Participants received written and verbal instructions. The task consisted of 30 trials. We measured the primary eye latency and decisive eye latency in milliseconds of the eye movement responses, hand latency in milliseconds and hand accuracy in degrees of the hand movement responses. The primary eye latency is the time between the start of a trial and the primary eye movement, and the decisive eye latency is the time between the stimulus disappearance and the onset of the decisive eye movement towards the target. The decisive eye movement is the eye movement response that has entered the area of interest in which the right basket was located. Hand latency is the time between the start of a trial and the finger release from the monitor. Hand accuracy is the distance of the finger touch on the monitor from the area of interest (target). The error rate is the percentage of trials in which subjects indicated the wrong basket.

Tapping Tasks

The visuomotor tasks include a reflex-based tapping task (i.e. pro-tapping), a planning-based tapping task (i.e. anti-tapping) and a memory-based tapping task (i.e. memory-tapping) (Verheij *et al.* 2012; Muilwijk *et al.* 2013) (for technical details, see de Boer *et al.* 2013). Participants had to perform 10 trials per each task. Participants had to start by fixating on a black circle in the middle of the screen. Participants had to tap on the red circle that appeared (pro-tapping), or on the opposite side where the red circle appeared (anti-tapping), or memorise the position of the red circle and then tap on the screen where the red circle had appeared (memory-tapping). In the memory-tapping task, a peripheral red circle flashed for 50 ms during the fixation period. We measured the eye latency, hand latency and hand accuracy. During the anti-tapping and memory-tapping tasks, the performance was measured with the percentage of incorrectly performed trials. In these trials, the subject made a reflexive eye movement towards the stimulus and was not able to suppress the eye movement (Muilwijk *et al.* 2013).

Statistical analyses

Recordings of eye and hand movements were analysed using a custom-made MATLAB script (MATLAB R2019b, MathWorks). Trials were excluded if the eye-tracking was poorly recorded (i.e. invalid data), if no eye movements were made or if the visual target was not seen (i.e. invalid performance) in the tapping tasks. Data points were excluded from further analyses if the values were more than ±2SD of the mean and showed an invalid performance (i.e. the visual target was not seen) after revision of the analyses (Verheij *et al.* 2012; Muilwijk *et al.* 2013). Participants were excluded from further analyses if less than two valid responses were measured to one of the visual stimuli of the Visual Threshold Task.

Statistical analyses were performed using IBM Statistics SPSS (version 25). All variables were tested for normality using the Kolmogorov–Smirnov test. Variables that had positive or negative skewness were transformed with a square root, or reflect and square root transformation, respectively. The control and NF1 groups were tested for significant differences in age, sleepiness and level of education using the non-parametric Mann–Whitney U test. Differences in

gender between groups were tested using the chi-square test. If one of these variables was significantly different between both groups, the variable was added as a covariate in further analyses. Differences between the groups in the eye and hand movement responses of each task were analysed with multivariate analyses of variance (MANOVAs). In the MANOVAs for the Visual Threshold Task, the dependent variables were reaction time to fixation and fixation duration and the independent variable was group (NF1 or control). In the MANOVAs for the Trajectory Prediction Task and Tapping Tasks, the dependent variables were the eye latency, hand latency and hand accuracy and the independent variable was group (Verheij *et al.* 2012; Muilwijk *et al.* 2013). Multivariate and univariate main effects were reported. Correlations between age, educational attainment and the outcome measures were evaluated using the non-parametric Spearman's correlation coefficients, and *P*-values were corrected for multiple testing with the Bonferroni correction. A *P*-value ≤ 0.05 was statistically significant.

Results

We included 22 adults with NF1 and 31 controls in our study. We had to exclude 18% of trials to calculate reaction time to fixation and fixation duration due to invalid data, no eye movements or invalid performance in the tapping tasks. We identified 3.3% of the data as outlier. We excluded two participants for the Visual Threshold Task due to lack of more than two valid responses ($n_{control}$ = 1, n_{NF1} = 1). Adults with NF1 and controls did not significantly differ in age (M_{NF1} = 28.9 ± 11.0; $M_{control}$ = 32.9 ± 11.1; U_{age} = 246.5, P = 0.09), gender (χ^2_{gender} = 0.03, P = 0.87) or sleepiness prior to the experiment (U_{KSS} = 162, P = 0.16). However, adults with NF1 showed a significant lower level of education than controls ($U_{education}$ = 139, $P < 0.001$) (Table 1). Therefore, the transformed level of education was added as covariate in the further analyses. Because education level was coded on a scale, we treated educational attainment as a continuous variable.

The Visual Threshold Task

Overall, no significant differences were found in reaction time to fixation and the transformed fixation duration between the control and NF1 groups in the Visual Threshold Task in all conditions (Table 2). This indicates that visual–spatial functioning was similar in both groups. Reaction time to fixation decreased with the difficulty to detection (Table 2).

The Trajectory Prediction Task

The NF1 group did significantly differ from the control group during the Trajectory Prediction Task ($F_{4,38}$ = 4.4, P = 0.005, Wilk's Λ = 0.69) (Table 2; Fig. 2a,b; adaptations of Fig. 2a,b are shown in Figs S1 and S2). Univariate tests showed that the NF1 group had a significantly shorter decisive eye latency than the control group ($F_{1,44}$ = 10.4, P = 0.002, eta^2 = 0.2), but no differences were found between the two groups in the transformed primary eye latency, hand latency and hand accuracy. Additionally, explorative analyses of the eye–hand latency revealed no significant effects between groups. The performance on the Trajectory Prediction Task did not differ between the groups ($Errorrate_{NF1}$ = 14% ± 21; $Errorrate_{control}$ = 11% ± 20).

Table 1 The demographics per group for controls and adults with NF1

Demographics	Control (*n* = 31)	NF1 (*n* = 22)
Age in years (mean ± SD)	32.9 ± 11.1	28.9 ± 11.0
Gender: Male in % (*N*)	38.7 (12)	40.9 (9)
Sleepiness (median, range)	2.0, 1–7	2.0, 1–6
Level of education (median, range)	6, 4–7	5, 1–6

NF1, neurofibromatosis type 1; SD, standard deviation.

Table 2 The eye and hand movement responses per group for controls and adults with NF1

	Control (*n* = 30)			NF1 (*n* = 21)		
Visual–spatial task[†] (median, IQR)	**RTF (ms)**		**FD (ms)**	**RTF (ms)**		**FD (ms)**
Contrast detection 100	253, 45		2583, 292	241, 55		2565, 565
Contrast detection 1.25	1019, 345		1422, 594	853, 541		1460, 1009
Motion coherence 100	441, 137		2358, 581	435, 136		2271, 825
Motion coherence 60	572, 304		1367, 533	519, 262		1363, 815
Form coherence 100	280, 57		1827, 603	280, 52		1827, 619
Form coherence 50	431, 137		1923, 766	447, 176		1871, 606
VT motion detection	341, 92		2538, 373	363, 87		2475, 450
Visuomotor tasks (mean ± SD)	**HL (ms)**	**EL (ms)**	**HE (°)**	**HL (ms)**	**EL (ms)**	**HE (°)**
Trajectory prediction pEL | dEL	754 ± 122	495 ± 41 | 598 ± 62*	0.75 ± 0.58	800 ± 184	471 ± 36 | 573 ± 67*	0.97 ± 0.79
Pro-tapping	342 ± 40	224 ± 20*	0.47 ± 0.12*	342 ± 42	205 ± 22*	0.56 ± 0.12*
Anti-tapping	415 ± 68	319 ± 90	2.56 ± 0.95*	426 ± 61	269 ± 66	3.56 ± 1.26*
Memory-tapping	538 ± 73	537 ± 222*	2.30 ± 0.58	580 ± 75	373 ± 193*	2.84 ± 0.45

*Significantly different between adults with NF1 and controls ($P < 0.05$).

[†]Only the results of the easiest option of difficulty (i.e. 100% difference) and the near-threshold option of difficulty (i.e. 1.25%, 60% and 50%, respectively) during the Visual Threshold Task are presented for contrast detection, motion coherence and form coherence.

NF1, neurofibromatosis type 1; IQR, interquartile range; VT, Visual Threshold Task; pEL, primary eye latency; dEL, decisive eye latency; RTF, reaction time to fixation; FD, fixation duration; HL, hand latency; EL, eye latency; HE, hand error in degrees; SD, standard deviation.

The Tapping Tasks

In the visuomotor tasks, the NF1 group did differ from the control group in the pro-tapping ($F_{3,43} = 8.3$, $P < 0.001$, Wilk's $\Lambda = 0.64$), the anti-tapping ($F_{3,45} = 5.4$, $P = 0.003$, Wilk's $\Lambda = 0.74$) and the memory-tapping tasks ($F_{3,43} = 4.4$, $P = 0.009$, Wilk's $\Lambda = 0.77$) (Table 2; Fig. 2a,b; adaptations of Fig. 2a,b are shown in Figs S1 and S2). In the pro-tapping and memory-tapping tasks, univariate tests showed significantly shorter eye latency in the NF1 group than in the control group ($F_{pro}(1,45) = 8.3$, $P = 0.006$, $eta^2 = 0.2$; $F_{memory-1,45} = 9.3$, $P = 0.004$, $eta^2 = 0.2$) (Fig. 2a). Additionally, in the pro-tapping and anti-tapping tasks, the hand accuracy was significantly less in the NF1 group than in the control group ($F_{pro}(1,45) = 11.5$, $P = 0.001$, $eta^2 = 0.2$; $F_{anti-1,47} = 11.4$, $P = 0.003$, $eta^2 = 0.2$; Fig. 2b), indicating a worsened hand accuracy in the NF1 group. The performance on the anti-tapping did not differ between the groups ($Errorrate_{NF1} = 82\% \pm 20$; $Errorrate_{control} = 70\% \pm 29$), indicating that both groups made a similar amount of reflexive eye movements towards the stimulus. In the memory-tapping task, the NF1 group did not differ from the control group in hand latency and hand accuracy (Table 2; Fig. 2). Interestingly, however, the performance on the memory-tapping was significantly worse in the NF1 group than in the control group, indicating that the NF1 group made more reflexive saccades prior to the disappearance of the visual stimulus ($Errorrate_{NF1} = 64\% \pm 30$; $Errorrate_{control} = 44\% \pm 33$; $U = 181.5$, $P = 0.03$). Additionally, explorative analyses of the eye–hand latency revealed no significant effects between groups in all tasks.

Correlations

There were no significant correlations between age and the eye and hand movement responses. However, educational attainment showed a significant correlation with hand latency in the memory-tapping tasks: a higher education attainment correlated significantly with a decrease of reaction time of hand latency ($r_{memory} = -0.4$, $P = 0.004$).

Discussion

Studying eye and hand movement responses using eye-tracking could be a non-invasive objective and quantitative assessment of the visual–spatial and

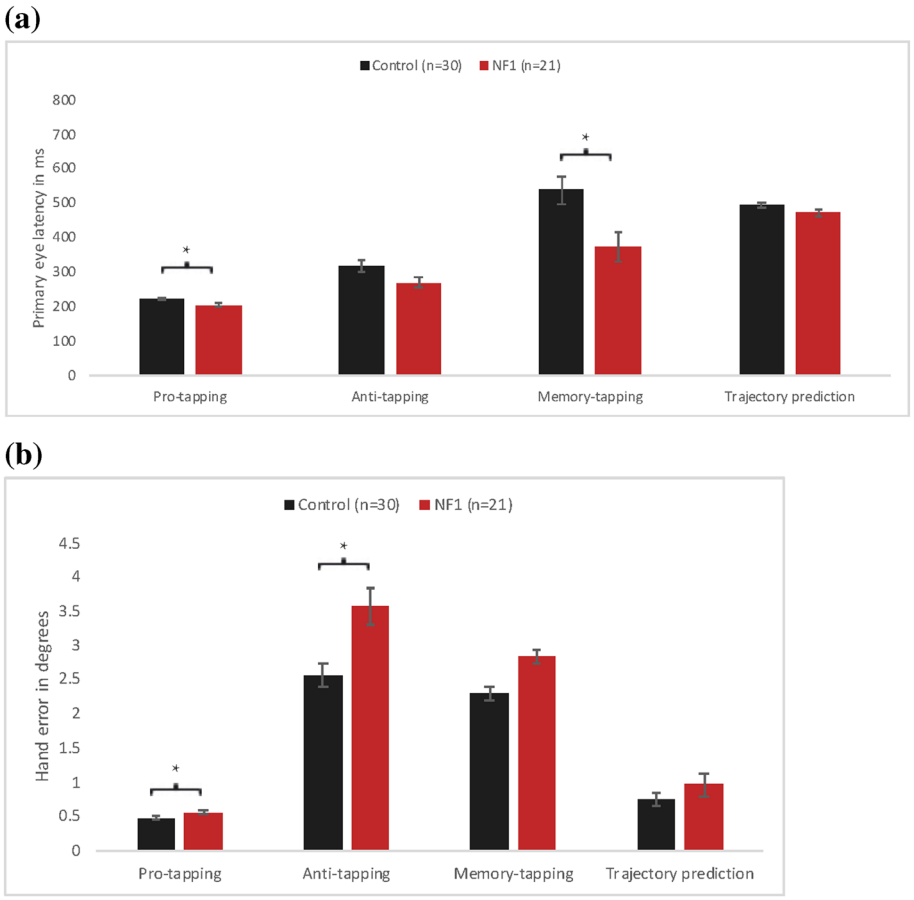

Figure 2. Eye movement responses and hand accuracy per visuomotor task per group. (a) Adults with neurofibromatosis type 1 (NF1) showed faster eye movement responses (eye latency) than controls in the visuomotor tasks; these findings were significantly different between groups in the pro-tapping and memory-tapping tasks ($F_{pro}(1,45) = 8.3$, $P = 0.006$, $eta^2 = 0.2$; $F_{memory\_\ 1,45} = 9.3$, $P = 0.004$, $eta^2 = 0.2$). (b) The hand error was significantly higher in the NF1 group than in the control group in the pro-tapping and anti-tapping tasks ($F_{pro\_\ 1,45} = 11.5$, $P = 0.001$, $eta^2 = 0.2$; $F_{anti\_\ 1,47} = 11.4$, $P = 0.003$, $eta^2 = 0.2$). Significance is displayed with asterisks.

visuomotor functioning in adults with NF1. Our findings showed no differences in primary visual–spatial information processing between the NF1 and control groups. However, the NF1 group had faster eye movement responses to visual stimuli than the control group, which was significant in the pro-tapping and memory-tapping tasks (primary eye latency), and the Trajectory Prediction Task (decisive eye latency). In the pro-tapping and anti-tapping tasks, these faster responses occurred with significantly reduced hand accuracy. Hand latency was not significantly different between the two groups in the visuomotor tasks.

In contrast to our expectations, the eye movement responses during the visual–spatial assessments did not differ significantly between groups. The Visual Threshold Task reflects the primary pathway of visual–spatial information processing. In this pathway, the retina projects the visual information via the lateral geniculate nucleus to the primary visual cortex (V1). V1 projects to the posterior parietal cortex (dorsal pathway) and to the inferior temporal cortex (ventral pathway), which are responsible for visual–spatial perception and visuomotor actions, and identification of visual stimuli, respectively. Clinically, VEPs measured with EEG are used to assess the function of the visual pathway from the eye to the visual cortex. VEP studies in children and adults with NF1 have shown abnormalities in the early components of the VEPs in 26–51% of people with

NF1, suggesting deficits to the primary visual pathway in NF1 (Jabbari *et al.* 1985; Iannaccone *et al.* 2002; Ammendola *et al.* 2006; Yerdelen *et al.* 2011; Nebbioso *et al.* 2020). Moreover, previous studies showed alterations in the Visual Threshold Task in reaction time to fixation and fixation duration in children with cerebral or ocular visual impairments (Pel *et al.* 2014). In the present study, we did not find abnormalities in these measures of primary visual information processing in our NF1 sample. Notably, all subjects in the present study had no ocular pathology. We also did not observe any deviations in the eye-tracking calibration recordings that might indicate visual problems. Additionally, previous studies in children with ADHD showed discriminating features in visual–spatial function compared to controls (Tseng *et al.* 2013; Itti 2015). Specifically, they showed gaze alterations in mixed directions in detecting contrast differences in texture and colour. Interestingly, ADHD symptoms are common comorbid problems in children with NF1 (Mautner *et al.* 2002). Our NF1 sample did not include clinically diagnosed ADHD patients, although symptoms could be subclinical because the existence of comorbidity of ADHD symptoms has been shown in adults with NF1 (Mautner *et al.* 2002). Overall, the present study showed no significant alterations in eye movement responses during primary visual information processing in an NF1 sample without ocular pathology.

However, adults with NF1 had a significantly shorter eye latency than controls during the visuomotor pro-tapping and memory-tapping tasks. The tapping tasks resemble the visual–spatial function of the Visual Threshold Task: identifying a visual stimulus, its location and visual and spatial relationships between objects, but the tapping tasks involve visuomotor integration. Previous studies using the pro-tapping task did not find any differences in eye latency between controls and patients with Parkinson's disease or Alzheimer's disease (Verheij *et al.* 2012; Muilwijk *et al.* 2013; Gorges *et al.* 2014; Molitor *et al.* 2015). However, patients with Parkinson's disease had faster eye movement responses in the anti-tapping task (de Boer *et al.* 2013). This could have been affected by alterations in the dopaminergic system. The dopamine system function seems also to affect cognition in NF1 mice (Diggs-andrews & Gutmann 2013). Furthermore, Kovarski *et al.* (2019) showed significantly faster eye movements on a pro-saccade task in children with autism spectrum disorder (ASD), which is in line with present findings. Interestingly, ASD symptoms are also common comorbid problems in children with NF1 (Garg *et al.* 2013). The saccades are thought to rely on a direct connection from the incoming visual stimulus to the motor command of the eyes (Edelman & Keller 1996; Munoz & Everling 2004). Because only relevant visual stimuli need to trigger saccades in everyday life, there is a decisive period between the visual input and motor processing that indicates the relevance of the stimulus. This is in accordance with hyper-reactivity to sensory input clinically observed in the NF1 comorbidities ASD and ADHD (Kovarski *et al.* 2019). Our findings suggest that hyper-reactivity to sensory input may also be present in adults with NF1. Additionally, the shorter decisive eye latency observed in the Trajectory Prediction Task in the NF1 group is in line with the hyper-reactivity hypothesis.

The shorter eye latency occurred with significantly reduced hand accuracy in the visuomotor pro-tapping and anti-tapping tasks in adults with NF1. It has been suggested that the visual dorsal pathway projects further to the prefrontal, premotor and medial temporal cortices (Kravitz *et al.* 2011). Hence, deficits in the visual dorsal pathway could lead to motor problems, which are known to be related to NF1 including deficits in fine motor skills (Johnson *et al.* 2010; Rietman *et al.* 2017). The shorter eye latency and reduced hand accuracy in the NF1 group resulted in a significantly reduced performance in the memory-tapping task. In the anti-tapping task, the performance seemed to be worse in the NF1 group than the control group, although these findings were non-significant due to high variability in the error rate. It is known that age could affect visuomotor ability, but we did not find any correlation between age and the outcomes. The groups were homogenous and the participants were not older than 55 years because the age of >55 years has been associated with cognitive decline affecting visuomotor ability (Li *et al.* 2021).

The lack of differences in the hand movement responses in the more complex visuomotor tasks is in contrast to our expectations. The Trajectory Prediction Task highly resembles the judgement of

line orientation task, which is commonly used in NF1. Impaired performance on the judgement of line orientation task has been shown in children and adults with NF1 (Levine *et al.* 2006; Pavol *et al.* 2006). Remarkably, the performance on the Trajectory Prediction Task did not differ between both groups in the present study. The similar performance in both groups may indicate that the Trajectory Prediction Task was not too difficult for the subjects. Notably, in the more complex visuomotor tasks, higher-order cognitive functions become involved and therefore involve other factors that influence the visuomotor function, including sensory perception, attention or intelligence. In our study, the sensory perception was not significantly different as assessed in the before-mentioned Visual Threshold Task. Furthermore, a previous study observed no abnormalities on attention tasks in adults with NF1, in contrast to findings in children with NF1 (Castricum, Tulen, Taal, *et al.* 2022). However, it is known that the intelligence quotient is lower-than-average for NF1 (Hyman *et al.* 2005; Krab *et al.* 2008; Ottenhoff *et al.* 2020). Interestingly, a reduced intelligence quotient was associated with reduced performance on various cognitive neurophysiological tasks in controls (Diaz-asper *et al.* 2004). Although we have not tested intelligence quotients and were unaware of the inclusion of adults with an intellectual disability in the present study, the NF1 group did show a significantly lower educational attainment than the control group. It is important to point out that the positive association between intelligence and educational attainment may be influenced by many other factors. In a previous study, a lower-than-average IQ was reported in a similar group of NF1 as the present study (Castricum, Tulen, Taal, *et al.* 2022). In the present study, we have added educational attainment as a covariate in all analyses. We did observe a significant negative correlation between educational attainment and the hand latency in the memory-tapping task, indicating that subjects with a lower educational level needed more time for visuomotor integration than subjects with a higher education level. Additional subgroup analyses based on the educational attainment were not performed due to the relative sample size and small variation in level of education. Future studies should confirm the finding of reduced hand latency in adults with NF1 and investigate whether hand latency could be a predictor of cognitive deficits.

A possible confounder of this study is ascertainment bias due to the potential overrepresentation of highly motivated or less severely affected adults with NF1. The lack of significant differences in the hand movement responses to the more complex visuomotor assessments could reflect this issue. Nevertheless, we did observe significant changes in the eye movement responses and hand accuracy of the NF1 group. The sample size was similar to previous studies that could indicate differences in eye movement responses between a neurological disorder and control behaviour (Verheij *et al.* 2012; Muilwijk *et al.* 2013) and to a previous study investigating visual information in NF1 adults showing reduced visual cortical plasticity (Castricum, Tulen, Heuvelmans, *et al.* 2022).

To our knowledge, this is the first study that measured eye and hand movement responses to quantify visual–spatial and visuomotor functioning in NF1 adults. Specific features of eye movement responses measured with eye-tracking have been shown to distinguish disorders with a neurodevelopmental basis from unaffected behaviour (Tseng *et al.* 2013). The present study provides more information on eye movement characteristics of adults with NF1. Furthermore, the experiments lasted only ~20 min, thereby minimising fatigue or diminished concentration. In addition, the tasks were simple and easy to understand, which make these quantitative eye movement and hand accuracy tasks attractive outcome measures in clinical intervention studies.

Abbreviations

ADHD	attention-deficit/hyperactivity disorder
ASD	autism spectrum disorder
KSS	Karolinska sleepiness scale
MANOVAs	multivariate analyses of variance
NF1	neurofibromatosis type 1
V1	primary visual cortex
VEPs	visual evoked potentials

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics approval statement

The Dutch Central Medical Ethics Committee of the Erasmus Medical Center Rotterdam approved the study following the Declaration of Helsinki (2013).

Patient consent statement

All subjects gave their written informed consent.

Data availability statement

Data are available from the corresponding author on reasonable request.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

Figure S1. Adaptation of figure 2a representing a boxplot with individual points. Eye movement responses per visuomotor task per group representing individual data points. All data were tested for normality before analyses were preformed. Adults with NF1 showed shorter eye-latencies than controls in the visuomotor tasks, these findings were significantly different between groups in the pro- and memory-tapping tasks ($F_{pro\_1,45} = 8.3$, $p = 0.006$, $eta^2 = 0.2$; $F_{memory\_1,45} = 9.3$, $p = 0.004$, $eta^2 = 0.2$). A. results on the pro-tapping task, B. results on the anti-tapping task, C. results on the memory-tapping task, D. results on the Trajectory Prediction Task.

Figure S2. Adaptation of figure 2b representing a boxplot with individual points. Hand accuracy per visuomotor task per group representing individual data points. All data were tested for normality before analyses were preformed. The hand error (HE) was significantly higher in the NF1 group than in the control group in the pro- and anti-tapping tasks ($F_{pro\_1,45} = 11.5$, $p = 0.001$, $eta^2 = 0.2$; $F_{anti\_1,47} = 11.4$, $p = 0.003$, $eta^2 = 0.2$). **A.** results on the pro-tapping task, **B.** results on the anti-tapping task, **C.** results on the memory-tapping task, **D.** results on the Trajectory Prediction Task.