Steady-State Visual Evoked Potentials in Children With Neurofibromatosis Type 1: Associations With Behavioural Rating Scales And Impact of Psychostimulant Medication

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Abstract

Background: Neurofibromatosis type 1 (NF1) is a genetic disorder often associated with cognitive dysfunctions, including a high occurrence of deficits in visuoperceptual skills. The neural underpinnings of these visuoperceptual deficits are not fully understood. We used steady-state visual evoked potentials (SSVEPs) to investigate possible alterations in the synchronization of neural activity in the occipital cortex of children with NF1.

Methods: SSVEPs were measured using electroencephalography and compared between children with NF1 (n = 28) and neurotypical controls (n=28) aged between 4 and 13 years old. SSVEPs were recorded during visual stimulation with coloured icons flickering at three different frequencies (6Hz, 10Hz and 15 Hz) and analyzed in terms of signal-to-noise ratios. A mixed design ANCOVA was performed to compare SSVEP responses between groups at the three stimulation frequencies. Pearson's correlations with levels of intellectual functioning as well as with symptoms of ADHD, ASD and emotional/behavioural problems were performed. The impact of psychostimulant medication on the SSVEP responses was analyzed in a subset of the NF1 group (n=8) with paired t-tests.

Results: We observed reduced signal-to-noise ratios of the SSVEP responses in children with NF1. The SSVEP responses were negatively correlated with symptoms of inattention and with symptoms of emotional/behavioural problems in the NF1 group. The SSVEP response generated by the lowest stimulation frequency (i.e., 6Hz) was rescued with the intake of psychostimulant medication.

Conclusions: Impaired processing of rhythmic visual stimulation was evidenced in children with NF1 through measures of SSVEP responses. Those responses seem to be more reduced in children with NF1 who exhibit more symptoms of inattention and emotional/behavioral problems in their daily life. SSVEPs are potentially sensitive electrophysiological markers that could be included in future studies investigating the impact of medication on brain activity and cognitive functioning in children with NF1.

Background

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder caused by pathogenic alterations in the NF1 gene. With an estimated prevalence of one in 3000, it is one of the most common inherited disorders affecting the human nervous system (1, 2). While NF1 affects multiple systems of the body, the most frequent complications experienced in childhood are cognitive dysfunction and behavioural problems (3).

Children with NF1 are at increased risk of developing several neurodevelopmental problems. Around 20% of children with NF1 meet diagnostic criteria for specific learning disorders (4), but up to 75% perform more than one standard deviation below their peers in reading, writing or mathematics-related skills (5). They are therefore much more likely to receive special education or remedial teaching throughout their schooling (5). The internalizing and externalizing behavior problems as well as the social difficulties experienced by children with NF1 can also impact their development and quality of life (6–8). In some

cases, social difficulties are related to a comorbid diagnosis of autism spectrum disorder (ASD), the incidence of which is estimated at 25% of children with NF1 (9–11).

Regarding specific domains of cognitive functioning, visuoperceptual deficits have been particularly studied and are considered a robust characteristic of the NF1 cognitive phenotype. In addition to the lower performance consistently found on the Judgement Orientation Line test (12), deficits in the perceptual analysis of shapes and their spatial features (13), impairments in visual learning (14, 15) and abnormal reactivity to visual signals (16) were evidenced using various cognitive tasks. Moreover, children with NF1 exhibit reduced visuomotor integration (17) and a high prevalence of motor problems (18).

Along with visuoperceptual skills, attention and executive functions are amongst the most frequently impaired cognitive domains in NF1. Behavioural symptoms consistent with the attention-deficit/hyperactivity disorder (ADHD) diagnosis are very common as well. Whether these symptoms result from ADHD as an independent comorbidity or are a consequence of NF1 is still a matter of debate (19). Nevertheless, between 38 and 67% of children with NF1 meet diagnostic criteria for ADHD (20, 21) and the comorbidity was shown to have a negative impact on the intellectual outcome and academic achievement (19, 22). As a result, a large proportion of children with NF1 are treated with methylphenidate, a psychostimulant medication often prescribed for ADHD due to its action on the dopaminergic and noradrenergic systems (23), or with other psychostimulant medications. Methylphenidate is thought to have beneficial effects on the cognitive performance of children with NF1 (24, 25), but the impact on measures of brain activity is still unknown in NF1.

Structural and functional brain abnormalities evidenced in patients with NF1 have helped to understand the neurobiological basis of the NF1 cognitive phenotype, particularly regarding visuoperceptual deficits. In an fMRI study, Clements-Stephens, Rimrodt (26) reported inefficient recruitment of the right hemisphere network and hypoactivation of the primary visual cortex in children with NF1 while performing the Judgment of Line Orientation task. Violante, Ribeiro (27) also found reduced activation of the low-level visual cortex in both children and adults with NF1 during magnocellular and parvocellular stimulations. Moreover, the authors found a deficient deactivation of the default mode network in response to magnocellular stimulation, which was hypothesized to be related to the attentional deficits in this population. In an EEG study, Ribeiro, d'Almeida (28) reported anomalies in the long-latency components of the visually-evoked potential in response to chromatic stimulation. They also found abnormal enhancement of alpha oscillations in the parieto-occipital cortex, which was related to increased attentional lapses in a visual detection task. A better understanding of the differences in the functioning of the occipital cortex in NF1 patients may therefore be useful in elucidating the visuoperceptual and attentional deficits in this population.

At the molecular level, reduced γ-aminobutyric acid (GABA) levels were evidenced in the occipital cortex of children with NF1 (29), which suggests an alteration in the balance between excitatory and inhibitory mechanisms in this brain region. GABA neuron-mediated inhibition plays an essential role in the

synchronization of neural activity and generation of brain rhythms (30). Synchronization of neural activity with external stimuli is a fundamental mechanism of sensory processing. It is thought to be involved in attentional selection and to modulate the strength of stimulus representation (31). Deficient GABAergic neurotransmission in NF1 could therefore lead to impaired synchronization of occipital activity, which could contribute to the emergence of visuoperceptual deficits.

In this study, we examined the synchronization of occipital activity in children with NF1 and neurotypical controls aged between 4 and 13 years old by measuring the electrophysiological response to the rhythmic delivery of visual stimuli at different frequencies using electroencephalography (EEG). EEG allows the investigation of visually evoked activity in a rapid and non-invasive way that is well suited for children. The periodic delivery of visual stimuli elicits a periodic neural response in the visual cortex, also known as steady-state visual evoked potentials (SSVEP). SSVEP appears in the EEG signal as a clear peak (or power increase) at the stimulation frequency and its harmonics. The generating mechanism of the steady-state response is a matter of debate, especially concerning its relationship with spontaneous (or endogenous) oscillatory activity. Nevertheless, it is thought to emerge from the synchronization of neural activity to the stimulus frequency via phase alignment (32). SSVEP cortical sources are found mainly in the primary visual cortex, but depending on the frequency of stimulation, contributions have also been identified from the frontal cortex and from extracortical structures (33). Since SSVEP responses have high signal-to-noise ratios and are robust to artifacts (33), they are particularly useful to study cerebral activity in young children. Maturational changes of the SSVEP response occur during childhood. In the occipital region, increases in magnitude values of the 5 hertz (Hz) SSVEP were seen until 8-11 years old, while phase alignment values reached their maximum in adulthood (34). Atypical steady-state responses have been found in various psychiatric disorders, including schizophrenia (35, 36) and depression (37), as well as in other neurodevelopmental disorders such as ADHD (38) and ASD (39). It is therefore relevant to investigate wether the possible SSVEP alterations in NF1 could be associated with behavioural symptoms of comorbid neurodevelopmental disorders or emotional problems.

Psychostimulant medication, such as methylphenidate and amphetamines, could have an impact on the SSVEP response. Functional imaging studies revealed that such medication strengthens the connectivity between the dorsal attention network and the thalamus, as well as between the thalamus and sensory regions such as the visual cortex, which suggests a modulation of sensory processing (40). In a study examining the effects of methylphenidate on various electrophysiological markers of sustained attention, Dockree, Barnes (41) found no significant effect on the SSVEP amplitude generated by a patterned stimulus flickering at a rate of 25 Hz. However, the impact of psychostimulant on SSVEPs generated by lower frequencies is still unknown.

Objective and hypothesis

Our main goal in this study was to evaluate the integrity of the SSVEP response in children with NF1. The SSVEP response may reflect the underlying molecular mechanisms that are altered in NF1 and could be

correlated with higher level cognitive functions, such as attention. It could therefore be a relevant marker to evaluate the effectiveness of treatments aimed at improving cognitive functioning in NF1.

First, we compared the SSVEP response between children with NF1 and typically developing children at three stimulation frequencies (6 Hz, 10 Hz, 15 Hz). We hypothesised that children with NF1 would show reduced SSVEP amplitude at all frequencies.

Secondly, we explored the associations between the SSVEP response and measures of intellectual and behavioural functioning. At the behavioural level, we looked more specifically at symptoms of ADHD, ASD and emotional problems. We hypothesised that lower SSVEP amplitude would be associated with increased symptomatology.

Thirdly, we investigated the impact of psychostimulant medication intake on the SSVEP response with the hypothesis that medication would increase SSVEP amplitude and thus normalise the EEG signal.

Methods

Participants

Thirty-one children with NF1 were recruited in collaboration with the Neurofibromatosis clinic at CHU Sainte-Justine. All met the revised diagnostic criteria for NF1 from the International Consensus Group on Neurofibromatosis Diagnostic Criteria (42). Children with a history of neurosurgery or taking anticonvulsants were excluded. NF1 participants taking psychostimulant medication were recruited and offered to come back to the laboratory for a second EEG without medication (after a 24-hour washout) within one month following the first visit. Three participants did not perform this second EEG without medication and were thus excluded from the analyses. As a result, 28 children with NF1, from 4 to 13 years old, were included in the EEG analyses.

Other medical conditions and comorbidities associated with NF1 were reviewed in patients recruited. Three NF1 participants presented with optic pathway gliomas, identified by an ophthalmological evaluation. Non-parametric tests were performed to ensure that the EEG measures of these participants were not significantly different from the rest of the NF1 group. Two participants had a history of seizures in early childhood, which subsequently resolved, two were diagnosed with intellectual disability, one with Tourette's syndrome and one with ASD. Fourteen children in the NF1 group were diagnosed with ADHD. Eight of them were taking psychostimulant medication and were tested with and without medication. An additional table shows the type and dosage of psychostimulant medication taken by these participants, as well as the time between the EEG recordings with and without medication (see Additional file 1).

Twenty-eight controls, also from 4 to 13 years old, were recruited through social media and posters in public libraries. Exclusion criteria included any neurological condition, psychological or developmental disorder and intake of medication. No significant differences were found between groups in terms of age and sex ratios, as well as in household income (see Table 1).

The study was approved by the hospital's research ethics board. All participants' parents provided written informed consent to participate and were free to withdraw at any point.

Table 1
Demographic, cognitive and behavioural characteristics of the NF1 and control groups

	NF1 group (N=28)	**Control group (N=28)**	**Group comparison**	
	Mean (SD or %)	*Mean (SD or %)*	*T-Test or X^2*	*p*
Age (years)	9.39 (2.41)	8.88 (2.41)	0.80	0.43
Sex (N females)	15 (53.57%)	13 (46.43%)	0.29	0.59
Household income ($CAN)	85 608.70 (32 610.29)	124 652.17 (96 939.35)	-1.83	0.08
IQ	89.00 (10.96)	108.61 (13.32)	-6.02	0.0000002
Conners 3				
Inattention Scale	68.23 (15.42)	53.52 (10.87)	3.89	0.0003
Global Index	65.31 (17.91)	53.43 (10.44)	2.83	0.007
SRS-2				
Total Score	58.50 (11.80)	48.39 (7.12)	3.88	0.0003
CBCL				
Total Problems	57.32 (11.23)	47.30 (9.92)	3.50	0.001

Note. IQ results are presented in standard scores. Results from the Conners 3, the SRS-2 and the CBCL questionnaires are presented in T-scores, with higher scores representing more symptoms.

Experimental protocol

Neuropsychological evaluation and parental questionnaires

Participants' intellectual functioning was assessed during a neuropsychological evaluation conducted by a graduate student in Clinical Neuropsychology. The Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV) was administered for children between four and five years old and the Wechsler Intelligence Scale for Children, Fifth Edition (WISC-V) for those between six and 13 years old. The subtests were administered in the recommended order and breaks were scheduled during the session. NF1 participants taking psychostimulant medication did the neuropsychological evaluation with medication on their first visit.

Parents completed questionnaires prior to or during the testing in order to assess behavioural symptoms of ADHD, ASD and emotional problems. ADHD-related behaviours were assessed using the Conners 3rd Edition–Parent (Conners 3-P), ASD-related behaviours using the Social Responsiveness Scale, 2nd Edition (SRS-2) and emotional/behavioural problems using the Child Behavior Checklist (CBCL).

EEG acquisition

EEG recordings were performed in a dark, electrically shielded and soundproof room at CHU Sainte-Justine, using 128 electrode nets (Electrical Geodesics System Inc., Eugene, OR, USA). Signals were acquired and stored in a G4 Macintosh computer using NetStation EEG Software (Version 4.5.4) and sampled at 1000 Hz. During recording, impedances were kept under 40 kΩ and Cz acted as the reference electrode. Visual stimuli were presented on a screen located at 60 cm from the participants' eyes. An eye-tacking device (Tobii T120) was used to monitor the children's gaze during the expriment. Children were instructed to remain calm, to limit movements and to look at the screen throughout the task. A research assistant remained in the room with the participants and reiterated those instructions if necessary.

Visual task

Visual stimuli consisted of 18 coloured icons appearing and disappearing (onset/offset pattern) at the center of the screen at a frequency of 6 Hz, 10 Hz or 15 Hz. Luminance has been normalized between the different icons. Stimuli were presented via E-Prime 2.0 (Psychology Software Tools Inc. Pittsburgh, PA, USA). Each 5 seconds trial displayed one icon at one frequency. Each block was composed of 6 trials (two at 6 Hz, two at 10 Hz, two at 15 Hz) presented in a pseudo-random order (see Figure 1). The task contained 9 blocks, with 5 seconds pause in between blocks showing a fixation cross, for a total duration of 5 minutes and 10 seconds. The visual stimuli were designed to be attractive and to enhance young children's attention during the task.

Analyses

Off-line EEG processing

Off-line signal processing and analyses were carried out using MATLAB R2018b (Mathworks, Inc., Natick, MA) and the EEGLAB toolbox v14 (43). A 0.5-150 Hz bandpass filter and a notch at 60 Hz were applied. Twenty-eight electrodes located around the neck and containing muscular artefacts were removed. Remaining noisy electrodes were removed using a semi-automatic procedure. First, electrodes with a standard deviation lower than 2 μV or higher than 200 μV were automatically excluded. Secondly, a visual inspection was performed and electrodes with sporadic behaviour were manually removed. Data was re-referenced to an average reference. Eye movement and cardiac artefacts were removed with a semi-automatic independent component analysis (ICA). Data was then segmented into 5 seconds epochs (from the onset of the stimulation to 5 seconds post-onset) that were visually inspected and rejected if containing significant artefacts. All participants met the requirement of having a minimum of 6 remaining epochs (30 seconds) in each condition after artifact rejection. The average number of ICA components rejected and the average number of artifact-free epochs kept in each stimulation frequency are shown in

Tables 2 and 3. No significant difference was found in these pre-processing indicators compared between the NF1 and control groups, as well as between the recordings with and without medication performed by a subset of NF1 participants.

Table 2
EEG pre-processing indicators in the NF1 and control groups

	NF1 (N=28)	**Controls (N=28)**	**Group comparison**	
	Mean (SD)	*Mean (SD)*	*T-test*	*p*
ICA components rejected	2.18 (1.19)	2.00 (0.86)	0.64	0.52
Artifact-free epochs				
6 Hz	13.68 (2.72)	12.89 (3.36)	0.96	0.34
10 Hz	13.43 (3.04)	12.89 (3.19)	0.64	0.52
15 Hz	13.29 (2.92)	12.75 (2.88)	0.69	0.49

Table 3
EEG pre-processing indicators in the subset of NF1 participants tested with and without medication

	NF1 with medication (N=8)	**NF1 without medication (N=8)**	**Group comparison**	
	Mean (SD)	*Mean (SD)*	*T-test*	*p*
ICA components rejected	2.38 (0.52)	2.00 (0.54)	1.43	0.20
Artifact-free epochs				
6 Hz	12.25 (2.05)	11.38 (1.69)	1.14	0.29
10 Hz	11.63 (3.25)	10.63 (2.34)	0.86	0.42
15 Hz	12.25 (2.49)	10.88 (2.17)	1.46	0.19

SSVEP analysis

Fast Fourier transforms (FFTs) were performed on each 5 seconds epoch and averaged for each stimulation frequency (6, 10 and 15 Hz). The resulting power spectrum had a frequency resolution of 0.5 Hz. SSVEP amplitude was compared between groups in terms of signal-to-noise ratios (SNRs). To obtain SNRs, we calculated the ratio between the amplitude at the stimulation frequency and the mean amplitude of both adjacent frequencies in a 1 Hz range, and then applied a logarithmic transformation.

Our region of interest for SSVEP analysis consisted of seven electrodes in the Oz region (E70, E71, E74, E75, E76, E82, E83). Spectral amplitudes were calculated for each electrode and then averaged for

statistical analyses. All participants had at least four remaining electrodes in the Oz region after pre-processing.

Behavioural measures

Behavioural symptoms recorded from the three parental questionnaires (Conners 3, SRS-2 and CBCL) were compared between groups and correlations with SSVEP responses were performed. For the SRS-2 and CBCL questionnaires, analyses were carried out on Total scores. Specific scales from the questionnaires were not systematically investigated in order to limit the number of statistical tests and because their associations with SSVEP measures were not supported by specific hypotheses. Since the Conners 3 questionnaire does not include a Total score, analyses were carried out on the Global Index which includes 10 items and is known as a sensitive measure of response to treatment and as a measure of general psychopathology (44). Given the known interaction between attentional processes and SSVEP amplitude (45), analyses were also performed on the Conners 3 Inattention scale.

Statistical analyses

Statical analyses were carried out using IBM SPSS, version 26 (IBM, Armonk, NY, USA). Normality of the distribution was verified using asymmetry and kurtosis values. Parametric tests were used since those values were all in acceptable ranges (i.e. asymmetry and kurtosis z-scores smaller than |1.96|), except for the comparison of EEG measures between participants with optic pathway gliomas and the rest of the NF1 group for which we used the non-parametric Mann-Whitney test. Homogeneity of variance was tested by Levene's test. Bonferroni corrections for multiple testing were applied when needed.

T-tests were performed to compare groups in terms of demographics, intellectual functioning and behavioural symptoms. Sex ratios were compared using the Chi-squared test. SNRs of the SSVEP response were compared between groups at the three stimulation frequencies using a mixed design ANCOVA, with group (NF1, control) as a between-subjects factor and frequency (6Hz, 10 Hz, 15 Hz) as a within-subjects factor. Knowing the effect of age on SSVEP amplitude (34), age was added in the analysis as a covariate. For the mixed ANCOVA, the assumption of homogeneity of regression slopes was verified and respected (i.e. no significant interaction between age and group). The assumption of sphericity was verified with Mauchly's sphericity test and respected since the test was non-significant. Pearson's correlations were performed to investigate whether SSVEP SNRs were associated with measures of intellectual functioning and behavioural symptoms. Paired t-tests were used to compare EEG measures in the conditions with and without medication. For this last analysis, we calculated the difference between the two conditions and verified the normality of the differences' distribution (46).

Results

Cognitive and behavioural measures

Mean scores and group differences in intellectual functioning and behavioural symptoms measured by parental questionnaires are shown in Table 1. As previously demonstrated (47), the NF1 group's mean IQ

scores was slightly below average and was significantly different from the control group's mean IQ which was in the upper limit of the average range.

Behavioural symptoms captured by parental questionnaires were significantly higher in the NF1 group for all selected scales and total scores. In the NF1 group, mean scores on the Conners 3 Inattention scale and Global Index fell above clinically significant cut-offs (above high average; T scores ≥ 63). As for the SRS-2 Total score and CBCL Total problems, NF1 participants' mean scores fell in the high average range (T scores between 57 and 63).

SSVEP responses

The non-parametric Mann-Whitney test was used to ensure that the EEG measures of the three NF1 participants with optic pathway gliomas did not differ from the rest of the group and could be included in the analyses. SNRs of the SSVEP responses were not significantly different when compared between participants with optic pathway gliomas (Mdn = 3.41, 3.07, 3.34 for the 6 Hz, 10 Hz, 15 Hz stimulation) and the rest of the NF1 group (Mdn = 4.52, 4.67, 4.53 for the 6 Hz, 10 Hz, 15 Hz stimulation) for either the 6 Hz stimulation (U = 31.00, p = 0.67), the 10 Hz stimulation (U = 18.00, p = 0.17) or the 15 Hz stimulation (U = 24.00, p =0.35). To support the conclusion that these three participants with optic pathway gliomas can be included in the analyses, an additional table showing where the SNR measures of these participants lie in the NF1 distributions is provided (see Additional File 2).

Averaged power spectra resulting from the FFTs are shown in Figure 2 for the NF1 and control groups at each visual stimulation frequency. Sharp peaks at the fundamental frequency (i.e. the stimulus frequency) and at its harmonics (i.e. multiples of the stimulus frequency) are evidenced in both groups. SSVEP responses were compared between groups with SNR measures, which take activity at the adjacent frequencies into account.

The mixed design ANCOVA confirmed that the covariate age was significantly related to the SSVEP SNRs (F (1, 53) = 22.24, p = 0.000018). After controlling for age, a main effect of group on SNR measures was found (F (2, 53) = 4.92, p = 0.031, partial η^2 = 0.085), with higher SNR in controls (Figure 3). The partial η^2 indicates a medium to large effect size.

No significant interaction was found between groups and stimulation frequencies (F (2, 106) = 1.90, p = 0.16, partial η^2 = 0.035). Post-hoc ANCOVAs were carried out to analyze the effect of group in each stimulation frequency individually. The covariate was significantly related to the SSVEP SNR in each stimuluation frequency (p < 0.01). A significant difference between groups was found in the 15 Hz stimulation only (F (2, 53) = 6.78, p = 0.012, partial η^2 = 0.11).

Relationship with IQ and behavioural symptoms

Exploratory correlational analyses were performed to identify possible relationships between SSVEP responses and measures of intellectual functioning or behavioural symptoms. No significant correlation was found between SSVEP SNRs and IQ in both groups. As for associations with behavioural measures,

one significant negative correlation was found in the control group between the SSVEP SNR at 10 Hz and the Conners 3 Inattention scale (r = -0.47, p = 0.023) (Figure 4). Increased symptoms of inattention were therefore associated with reduced SNRs of the SSVEP at 10 Hz.

Similarly, in the NF1 group, SSVEP SNRs at 10 Hz were negatively correlated with the Conners 3 Inattention scale (r = -0.49, p = 0.011), but also with the Conners 3 Global Index (r = -0.46, p = 0.019) (Figure 5). SSVEP SNRs at 15 Hz also decreased with increasing symptoms on the Conners 3 Inattention scale (r = -0.55, p = 0.004) and Global Index (r = -0.49, p = 0.012) (Figure 6). In addition, the SSVEP SNRs at 15 Hz had a negative relationship with the CBCL Total problems (r = -0.54, p = 0.003) (Figure 7).

Considering the large number of exploratory correlations, Bonferroni adjustment for multiple comparisons would set statistical significance at 0.004. It should be noted that only the relationships found in the NF1 group between the SSVEP SNRs at 15 Hz and both the Conners 3 Inattention scale and the CBCL Total problems would remain significant with this adjustment.

ADHD comorbidity

Given the many associations of SSVEP amplitude with inattention symptoms, we investigated how the inclusion of NF1 patients with a comorbid ADHD diagnosis (N = 14) could have affected our findings. To do so, we divided our NF1 participants according to the presence or absence of a comorbid ADHD diagnosis and performed our main analysis (mixed design ANCOVA) with three groups (controls, NF1 with ADHD, NF1 without ADHD). The main effect of group on SNR measures was still significant (F (2, 52) = 3.87, p = 0.027, partial η^2 = 0.130) with a medium to large effect size. However, post hoc comparisons with Bonferroni adjustment revealed a significant difference solely between the control and NF1 with ADHD groups (p = 0.023) with higher SSVEP SNRs in controls. The NF1 without ADHD group did not differ from controls (p = 0.89) nor from NF1 participants with ADHD (p = 0.32).

Impact of psychostimulant medication

Paired t-tests were used to compare SSVEP responses in children with NF1 that are taking psychostimulant medication and who did the EEG recording with and without medication (N=8). On average, children with NF1 showed higher SSVEP SNR at 6 Hz with psychostimulant medication (M=4.97, SE=0.41) than without medication (M=3.48, SE=0.57) (t (7) = 3.27, p = 0.014, r = 0.78). No significant impact of the psychostimulant medication intake was found for the 10 Hz (t (7) = - 0.07, p = 0.94, r = 0.03) and 15 Hz stimulations (t (7) = 1.68, p = 0.14, r = 0.54) (Figure 8). The effect of medication on the SSVEP SNR at 6 Hz remains significant after Bonferroni adjustment for multiple comparisons which would set statistical significance at 0.017.

Since the impact of psychostimulant medication was investigated with a limited number of participants, the data was also analyzed in a descriptive manner, as shown in Table 4. For the 6Hz and 15 Hz stimulations, SNRs systematically increase with the intake of medication, except for one participant who presented multiple diagnoses (i.e. intellectual disability, ADHD, Tourette's syndrome). At 10 Hz, the impact

of psychostimulant medication is rather uncertain, with three participants showing decreased SNRs after the intake of medication.

Table 4
Individual SSVEP SNRs from the EEG recordings without (left column) and with (right column) medication in eight participants with NF1

Participants	SNR at 6 Hz (dB)		SNR at 10 Hz (dB)		SNR at 15 Hz (dB)	
N	*w/o*	*w*	*w/o*	*w*	*w/o*	*w*
1	2.94	4.65	3.07	1.38	0.72	2.01
2	4.88	3.73	3.92	1.62	5.23	3.69
3	4.61	6.52	2.70	1.14	1.58	2.23
4	5.08	6.37	4.80	4.93	4.50	4.93
5	4.52	6.02	1.18	1.53	2.60	3.27
6	0.36	3.93	0.52	2.92	1.08	6.02
7	2.72	4.06	4.66	5.76	4.20	4.38
8	2.71	4.47	5.19	6.41	4.53	6.95
Mean	3.48	4.97	3.25	3.21	3.05	4.18

Discussion

In this study, we identified altered SSVEP responses in children with NF1 aged between 4 and 13 years old. We analyzed the SSVEP generated by coloured icons flickering at three different frequencies (6Hz, 10 Hz and 15 Hz). Participants with NF1 showed clear peaks with maximal amplitude at the frequency of stimulation, but the SNRs of these peaks were decreased when compared to neurotypical controls. The SSVEP SNRs were not related to the level of intellectual functioning but were significantly correlated with behavioural symptoms captured by parental questionnaires. SNRs were predominantly correlated with inattention symptoms measured by the Conners 3, but also with emotional and behavioural problems measured by the CBCL. Moreover, our results show that the difference in SSVEP SNRs is increased in the subset of NF1 patients with comorbid ADHD. Finally, an increase in the SNR at 6 Hz was seen with the intake of psychostimulant medication in participants with NF1.

Reduced SSVEP responses in NF1

Reduced SSVEP responses in the NF1 group could result from structural and molecular abnormalities that have been identified in brain regions that underlie visual perception. In a MRI study of 39 participants with NF1 and 60 non-affected individuals, Duarte, Ribeiro (48) used a multivariate data-driven classification approach to identify the most relevant brain regions that allowed discrimination between

groups. Among those regions were the visual cortex and thalamus which showed characteristic structural differences. Thalamic hypometabolism has also been evidenced in children with NF1 (49). While SSVEP originates in the primary visual cortex (33), the thalamus also plays an important role in visual processing by not only acting as a relay of visual information from the retina to the visual cortex, but also by influencing the spatial and temporal dynamics of the visual signal (50).

At the molecular level, reduced SSVEP responses in NF1 could also reflect improperly balanced excitation and inhibition resulting from deficient GABA levels found in those same regions (51). After having found reduced GABA levels in the visual cortex of children and adolescents with NF1 (29), Violante, Patricio (51) showed that these deficits persist into adulthood, with lower concentration of GABA found in the occipital cortex and frontal eye fields. In addition, decreased binding of $GABA_A$ receptors were found in the parieto-occipital cortex, midbrain, and thalamus of adults with NF1. SSVEP responses emerge from the synchronization of large neuronal populations and are therefore likely to be disturbed by imbalances in excitatory-inhibitory neurotransmission across regions involved in visual processing.

Relationship with IQ and behavioural symptoms

The NF1 group's mean level of intellectual functioning was slightly below average and significantly lower compared to the control group. This result is congruent with the numerous studies showing a small downward shift in mean IQ scores, which are mostly found around the low average to average range (12). It is however unlikely that these different levels of intellectual functioning can explain the discrepancy evidenced in our electrophysiological measures. Indeed, our correlational analysis revealed no association between SSVEP SNRs and IQ in our sample. A comparable result was found in another EEG study investigating visual processing in NF1 that showed no correlation between IQ scores and electrophysiological measures which, in their case, were the amplitude of the visually evoked potentials and the amplitude of alpha oscillations (52).

Our SSVEP measures were however significantly related with behavioural symptoms measured through parental questionnaires. In controls, only smaller SNR resulting from the visual stimulation at 10 Hz was related with greater inattention symptoms. In NF1 participants, smaller SSVEP responses at 10 Hz and 15 Hz were correlated with higher inattention symptoms and higher scores on a global scale of ADHD-related symptoms (e.g. distractibility, agitation, impulsivity, emotional lability, etc.) measured by the Conners 3. However, among these associations with Conners 3 scores, only the relationship between SSVEP at 15 Hz and inattention symptoms in NF1 participants remains significant after adjusting for multiple comparisons. Endogenous attention is known to modulate SSVEP amplitude and phase coherence. In experimental protocols where two stimuli flickering at different frequencies are presented simultaneously, the shift of attention towards one stimulus was shown to enhance the power of the SSVEP generated by the attended stimulus (31, 45, 53, 54). In our study, different stimulation frequencies were presented sequentially, rather than simultaneously, which did not require participants to voluntarily shift their attention during the task. However, the optimal processing of the different colored icons presented at varying frequencies requires effective adaptation of the neural population's activity and synchronization, which appears to be more affected in children who show increased attentional problems in daily life.

In children with NF1, the SSVEP response resulting from the 15 Hz stimulation was also negatively related with symptoms of emotional/behavioural problems measured by the CBCL questionnaire and this correlation survived correction for multiple comparisons. The CBCL Total problems scale combines symptoms of internalizing and externalizing problems, as well as symptoms of attention, social and thought problems. In a study investigating emotional and behavioural problems in a large sample of children and adolescents with NF1 (N = 183), a mean score of 58.3 (± 10.3) on the CBCL Total problems was reported, which is in line with our results indicating a mean score of 57.3 (± 11.2) (55). Interestingly, in another study using the same questionnaire, these emotional/behavioural problems were found to be significantly increased in children presenting with the NF1-ADHD comorbidity when compared to NF1 children without ADHD (56). Our results thus suggests that the neural response to the 15 Hz stimulation covaries with a wide range of emotional/behavioral difficulties in children with NF1, which in turn might be related to the severity of ADHD symptomatology.

Finally, no correlation was found between the EEG measures and ASD-related symptoms in our sample. The severity of the ASD symptomatology in our NF1 group is consistent with most previous findings in the literature. In a population-based study of over 100 children with NF1 aged from four to 16 years, the mean total score reported on the SRS was between the high average and superior to average range (T score around 63)(57), while a mean score in the high average (T score = 58.5) was found in our study. Given the sensory processing abnormalities and GABAergic dysfunction also evidenced in ASD, the integrity of the steady-state response has been studied in this population. Two studies have reported reduced SSVEP amplitudes in the occipital region of children with ASD, one regarding the SSVEP first harmonic (58) and the other, at the second harmonic (39). However, further investigation is needed to determine whether these markers of sensory processing alterations vary with the severity of ASD symptoms in NF1. Interestingly, sensory processing differences in the auditory modality were evidenced in infants with NF1 and found to be related to later ASD traits (59).

ADHD comorbidity

Half of children part of the NF1 group previously received a medical or neuropsychological diagnosis of ADHD. This proportion is in line with the prevalence generally reported in the literature, with rates ranging from 38 to 67% of children with NF1 meeting diagnostic criteria for ADHD (19, 20, 60). Our results showed that, when considering the ADHD comorbidity in NF1 participants, group differences in SSVEP responses are only found between the NF1 with ADHD subgroup and controls. .

A very limited number of studies have examined the steady-state response in children with ADHD. Khaleghi, Zarafshan (38) investigated the auditory and visual steady-state response in adolescents with ADHD and adolescent controls when performing a motor response inhibition task. In the visual modality, adolescents with ADHD showed higher SSVEP amplitudes at the prefrontal and frontal regions, but lower amplitudes at the temporal and occipital regions. One way of interpreting their results was to suggest an abnormal connectivity between the anterior and posterior regions of the brain that could demonstrate deficits in the functional networks of frontoparietal and dorsal attention. While our experimental protocol

did not require children to perform a specific task during the visual stimulation, our results are consistent with their findings with regards to the occipital region.

The ADHD comorbidity in children with NF1 has been shown to have an adverse influence on the cognitive profile (19, 61) and adaptative functioning (62). Whether the greater difference on our electrophysiological measures is strictly attributable to the presence of an ADHD comorbidity in our NF1 participants or whether it is a consequence of more severe neurological deficits resulting from the NF1 mutation needs to be further investigated. However, given the high prevalence of ADHD in children with NF1, it is certainly relevant to include participants presenting with this comorbidity in our analyses. Moreover, our results support the perspective of NF1 as a valuable model to study the neural correlates that may underlie ADHD symptomatology.

Impact of psychostimulant medication

Studies have identified neurochemical alterations underlying the attentional system dysfunction in mouse models of NF1. Decreased exploratory and attentional behaviours in Nf1 +/− mice were found to be a consequence of reduced striatal dopamine, and both the neurochemical and behavioural deficits were reversed by treatment with methylphenidate (63, 64). In children with NF1, treatment with methylphenidate was shown to improve performance on a computerised attention task (56) and to reduce parent-reported ADHD symptoms (25). However, the impact of psychostimulant medication on markers of brain activity and sensory processing remains unknown in NF1. In our study, we explored how the psychostimulant medication, taken by a subset of the NF1 group (N=8), would affect the steady-state response.

Our results showed a significant increase in the SSVEP response generated by the 6 Hz stimulation with the intake of psychostimulant medication. The absence of significant impact on the SNRs of the 10 Hz and 15 Hz SSVEPs could indicate that synchronization of neural activity at higher frequencies is more severely affected by the imbalances in neurotransmission found in NF1 and thus less easily restored with psychostimulant medication. Interestingly, the 6 Hz SSVEP was also the only experimental condition where no correlation was found with any of the behavioural symptoms, which supports the idea that the neural responses to higher frequency stimulation are more closely related to the severity of the phenotype. It is also possible that the neural response to the 6 Hz stimulation is more sensitive to top-down attentional modulation and thus more reactive to the intake of psychostimulant medication that sthrenghtens connectivity of the attentional networks (40).

Limitations and perspectives

Limitations of this study include the relatively small sample size, especially for the investigation of the simulant medication’s impact on the EEG measures. More participants will be needed to confirm the absence of effect from medication intake at higher frequencies and to determine if different types of medication (e.g. lisdexamfetamine vs methylphenidate) induce dissociable effects on the EEG measures. Furthermore, adding a group of participants with a diagnosis of ADHD only (without NF1) would be relevant to determine if their electrophysiological profile is dissociable from that of children with NF1, and

if the associations found between SSVEP responses and inattention symptoms are specific to the NF1 diagnosis. Our control group's mean IQ scores were found in the upper limit of the average range, which could be due to a recruitment bias. Although no correlation was found between SSVEP responses and IQ, it may be interesting to compare NF1 and controls' SSVEP responses with IQ matched samples. Another limit of the study would be the absence of neuropsychological tests assessing the participants' visual attention abilities. We have shown that children's neural response was related to the severity of inattention symptoms exhibited in daily life, but it would be relevant to see if it also covaries with their performance on cognitive tests of attentional skills. Moreover, it would be interesting to see how the modulation of attention during the visual stimulation, with a Posner cueing paradigm for example, affects the steady-state response in children with NF1. A passive task with attractive visual stimuli, as we used in our study, is however well suited for young children and allowed us to obtain quality recordings with our participants as young as four years old. It bears repeating that no significant difference was found between groups in terms of pre-processing indicators (number of ICA components and epochs rejected). Therefore, group differences in SSVEP responses can not be explained by reduced quality of the EEG recordings in one group or the other.

Conclusions

In conclusion, visual processing abnormalities were identified in children with NF1 using SSVEP measures. The reduced SSVEP responses found in NF1 suggest decreased synchronization in the activity of neuronal populations in the visual cortex, which could be a consequence of neurochemical dysfunction, notably in the GABAergic system, and structural abnormalities in the visual cortex and thalamus. Our EEG measures seemed to be correlated with ADHD-related symptoms as well as with emotional/behavioural problems exhibited by children with NF1 in daily life. Moreover, the intake of psychostimulant medication in a subset of the NF1 group improved the SSVEP response resulting from the visual stimulation at the lowest frequency (i.e. 6 Hz). Taken together, these findings indicate that SSVEP measures have the potential to be sensitive EEG biomarkers to be included in translational studies and clinical trials aimed at restoring alterations in brain activity resulting from pathogenic variants in the NF1 gene.

Abbreviations

NF1: Neurofibromatosis type 1

ADHD: Attention deficit hyperactivity disorder

ASD: Autism spectrum disorder

fMRI: Functional magnetic resonance imaging

EEG: Electroencephalography

GABA: Gamma-aminobutyric acid

SSVEP: Steady-state visual evoked potential

SNR : Signal-to-noise ratio

Hz: Hertz

FFT: Fast Fourier Transform

Conners 3-P: Conners 3rd Edition–Parent

SRS-2: Social responsiveness scale, 2nd edition

CBCL: Child behavior checklist

IQ: Intellectual quotient

Declarations

Ethics approval and consent to participate

The research protocol was approved by the CHU Sainte-Justine Research Ethics Board. Procedures were explained to participants and their parents or guardians, and all provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

NF1 participants' EEG data is available in the Additional file 2. Other data used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

EL participated in the study design, coordinated the study, recruited the participants, carried out data collection and analysis, interpreted the data and drafted the manuscript. ARCP participated in the coordination of the study, recruitment of participants and data collection. KA helped implement the visual task, designed the EEG analysis tools, generated the EEG power spectra, and helped interpret the data. ISK participated in the study design and helped implement the visual task. EJ and LM conceived the visual task, reviewed the manuscript and contributed to the interpretation of the results. SP allowed the recruitment of patients from the Neurofibromatosis clinic at CHU Sainte-Justine and helped, as an expert on NF1, in understanding the clinical manifestations and other medical conditions of our NF1 participants. SL conceptualised and designed the study, helped interpret the data and draft the manuscript, and obtained fundings for the research. All authors have revised the manuscript and approved the final version.

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Figures

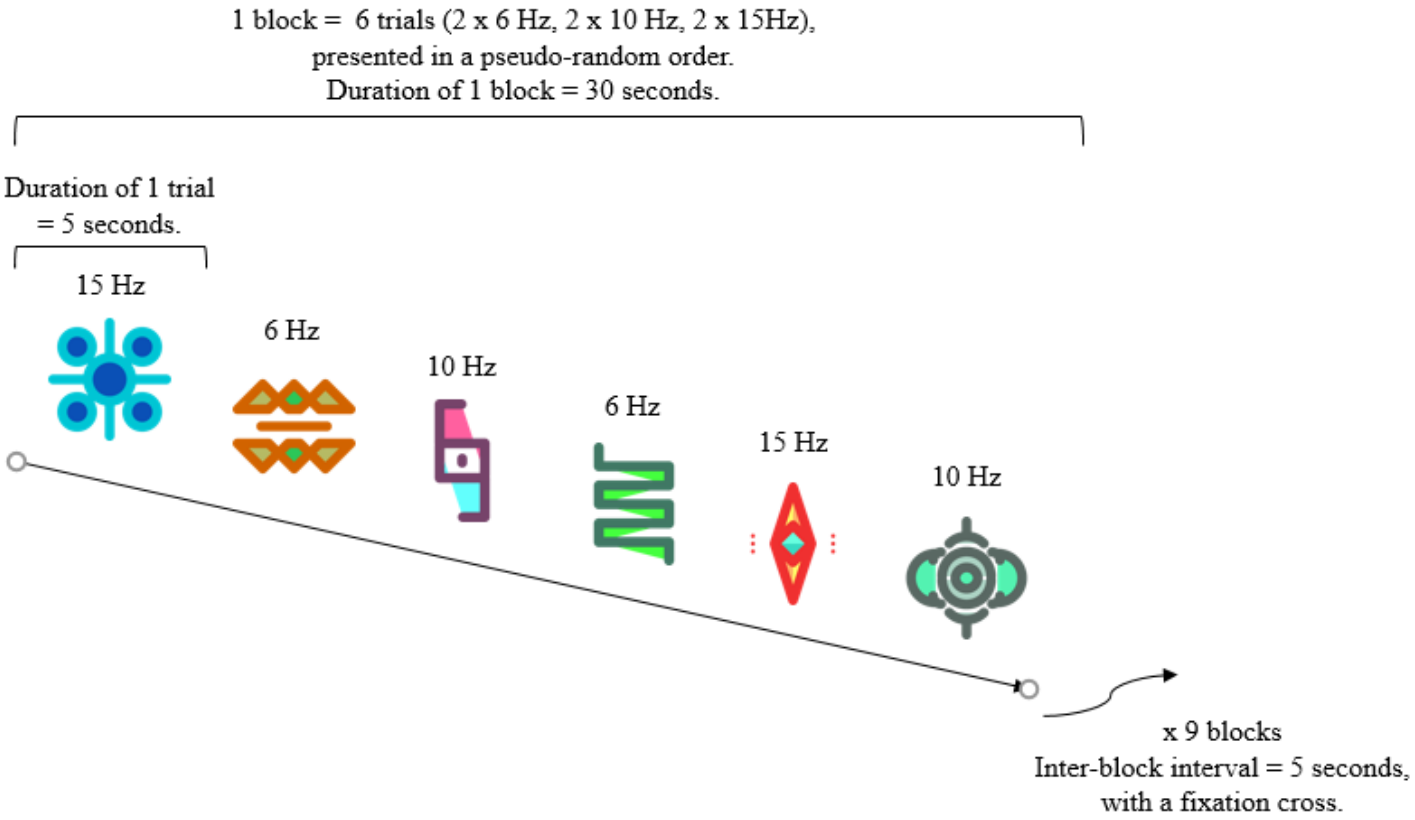

Figure 1

Design of the visual stimulation task.

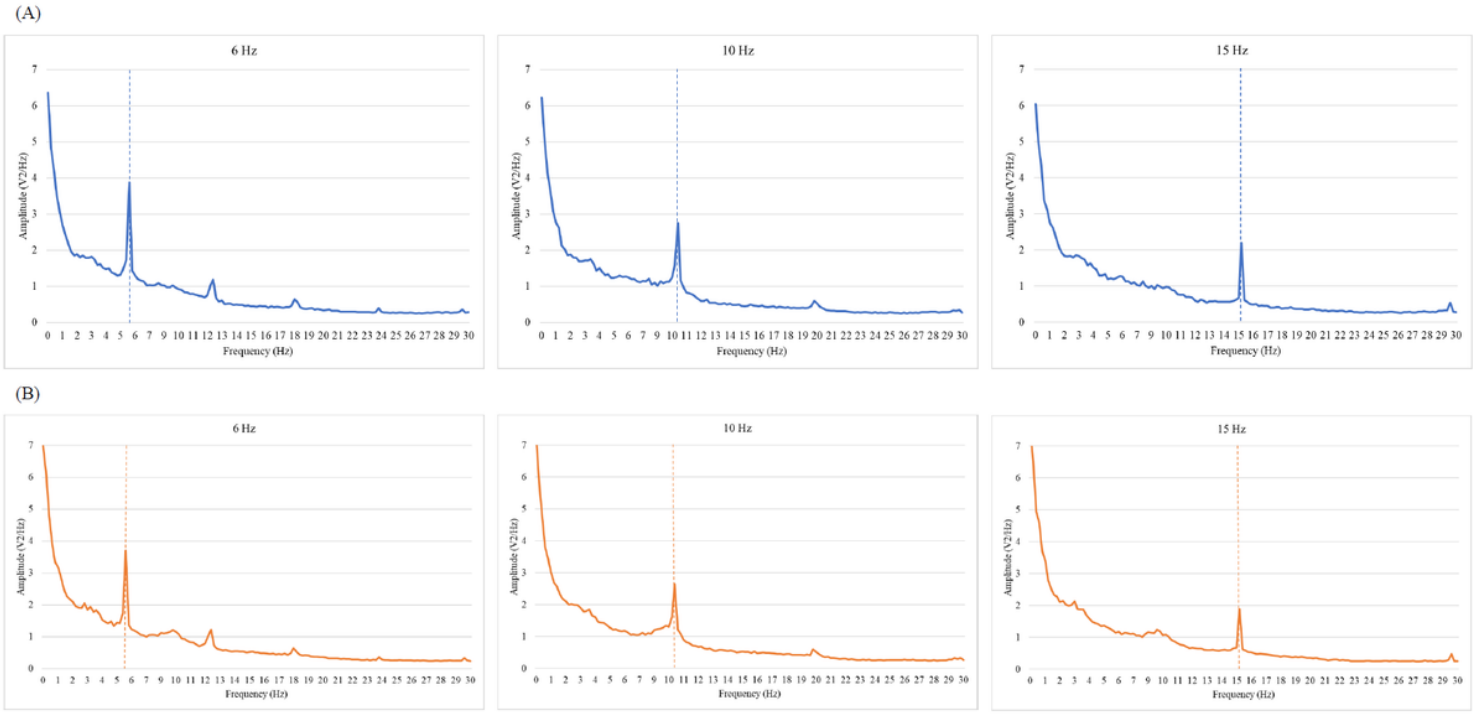

Figure 2

Averaged power spectrum resulting from the Fast Fourier Transforms in the control group (A) and NF1 group (B) for each stimulation frequency (6, 10 and 15 Hz). Dotted lines indicate the frequency of the visual stimulation at which the amplitude value was extracted.

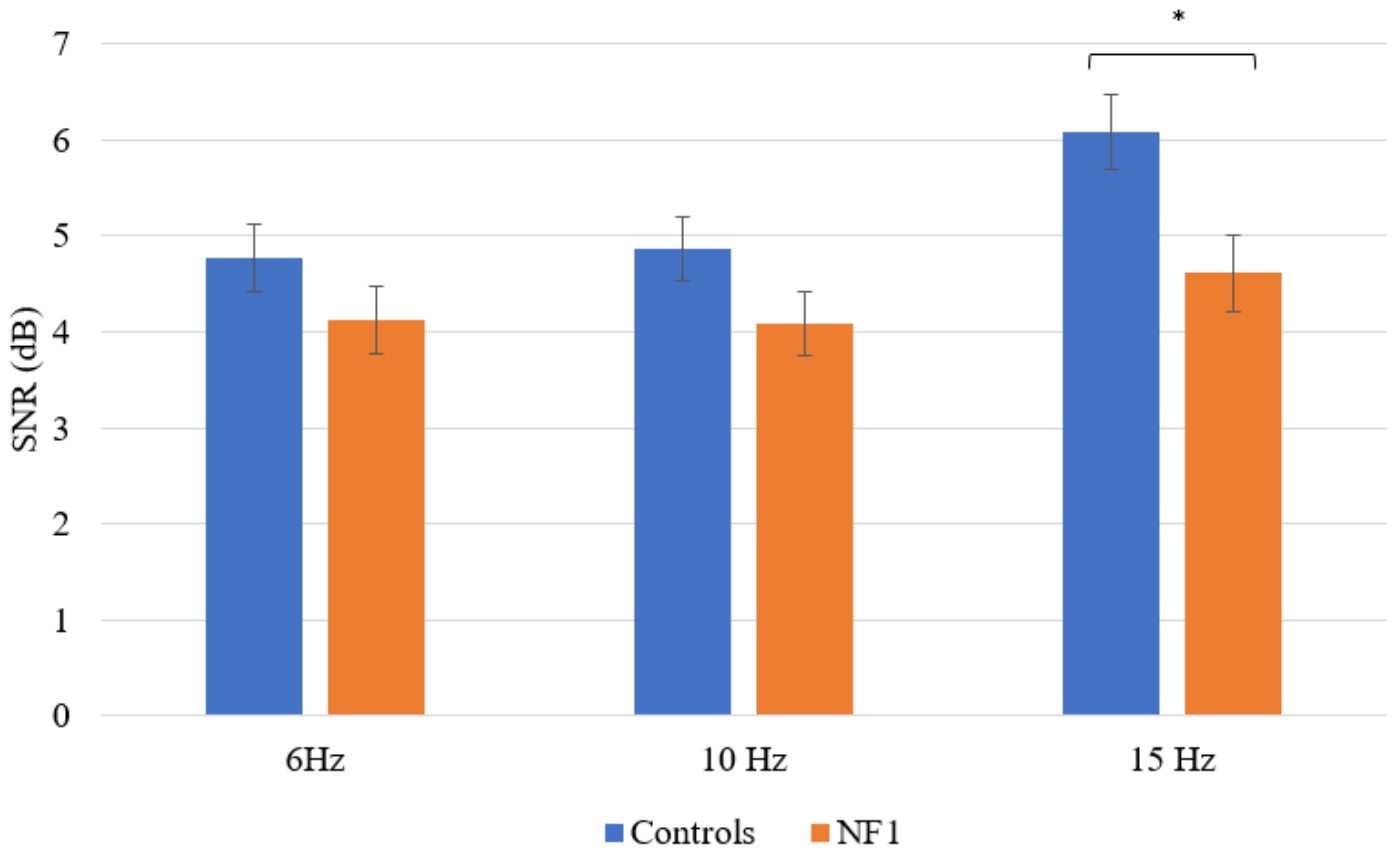

Figure 3

SSVEP SNR adjusted means (with standard errors as error bars) at each stimulation frequency by group. A main effect of group was found ($p < 0.05$) with lower SNRs in the NF1 group. Post-hoc analyses in each stimulation frequency revealed a significant difference between groups for the 15 Hz stimulation. *$p < 0.05$.

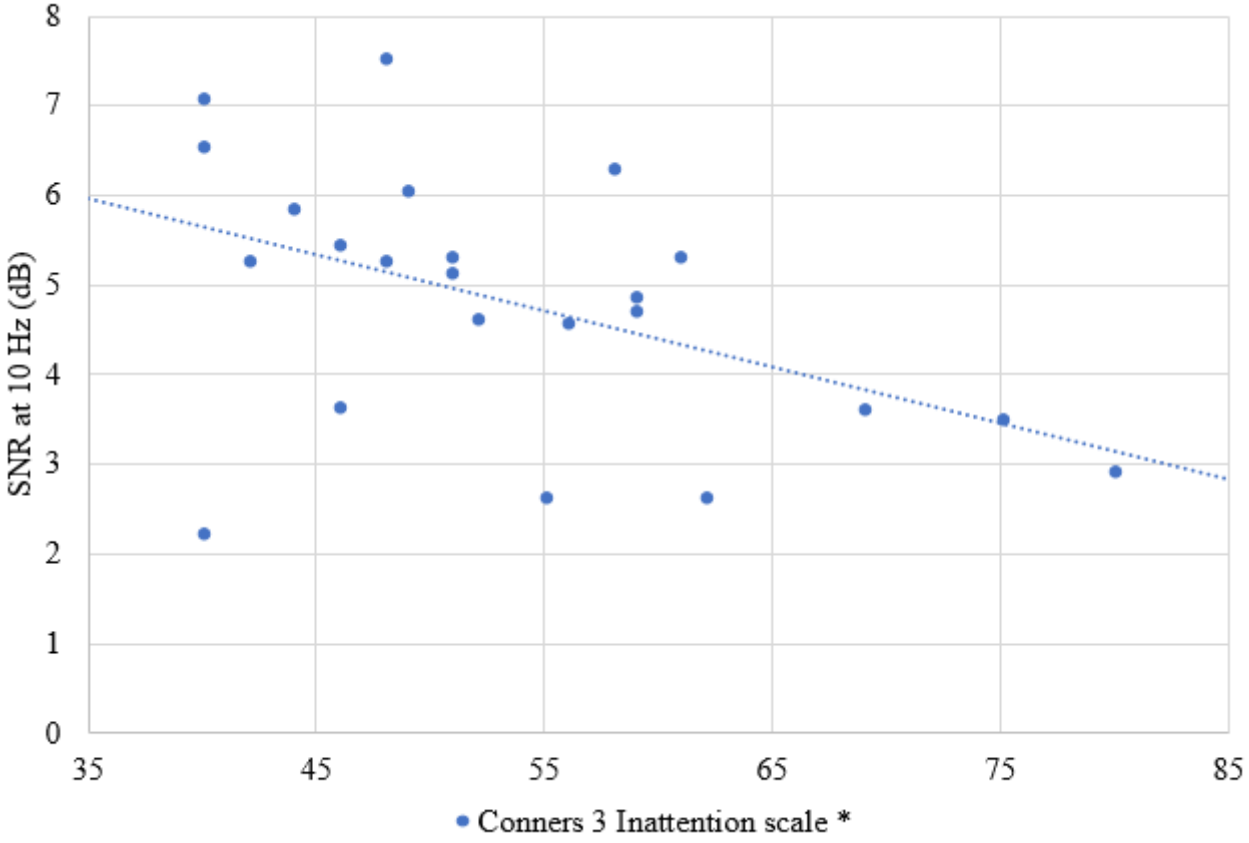

Figure 4

Relationship between the SSVEP SNR at 10 Hz and the Conners 3 Inattention scale in the control group. *p < 0.05.

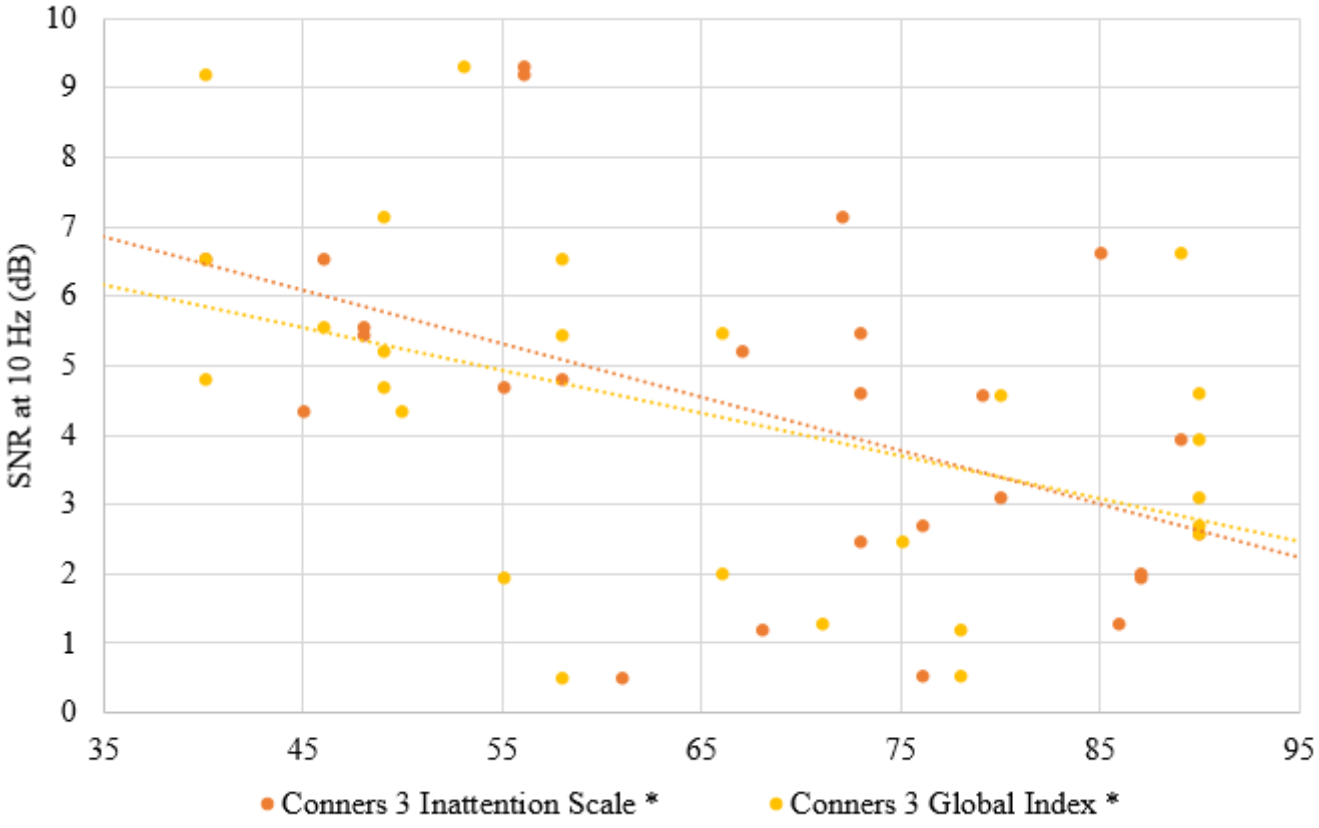

Figure 5

Relationship between the SSVEP SNR at 10 Hz and the Conners 3 Inattention scale and Global Index in the NF1 group. *p < 0.05.

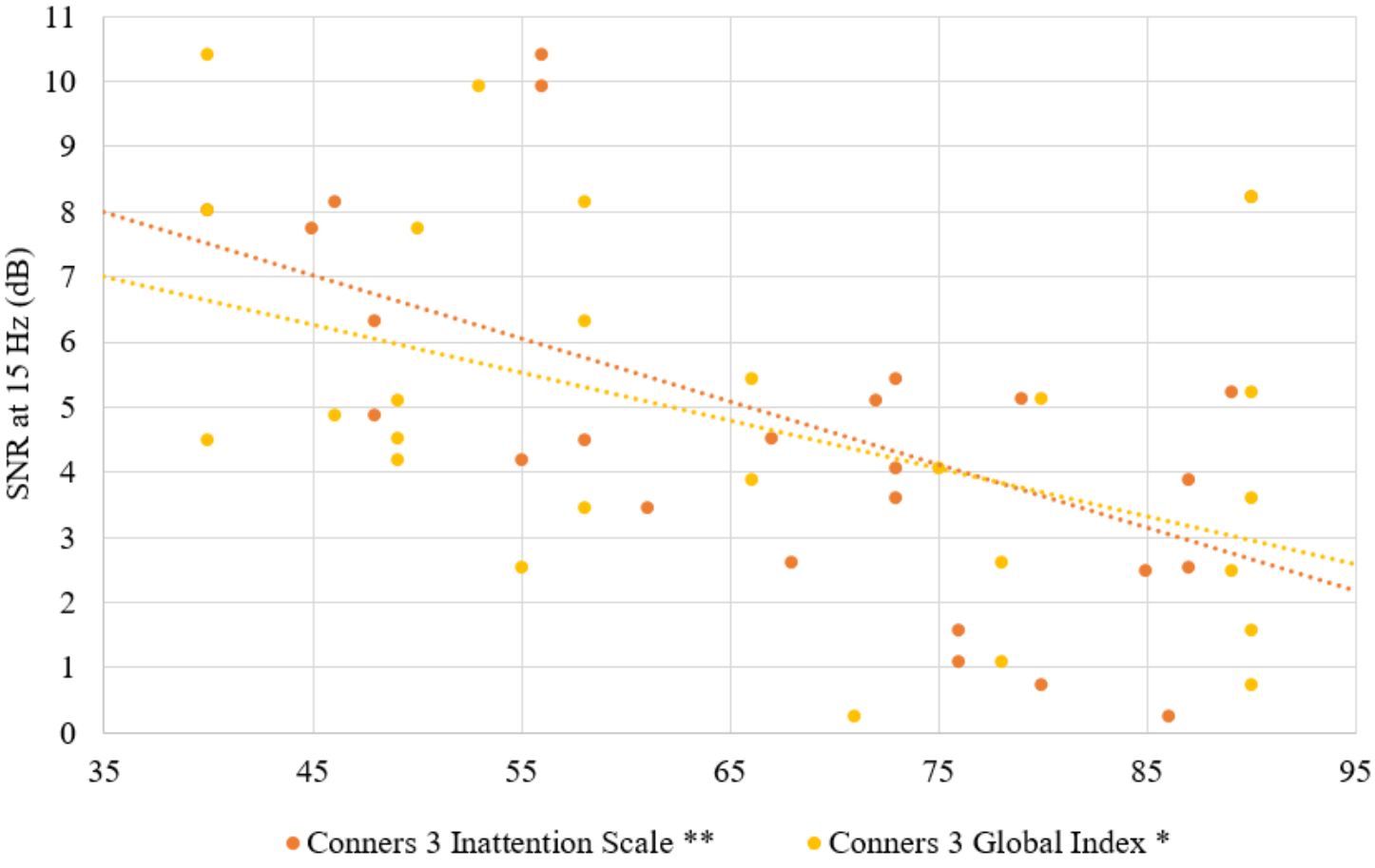

Figure 6

Relationship between the SSVEP SNR at 15 Hz and the Conners 3 Inattention scale and Global Index in the NF1 group. *p < 0.05; **p < 0.01.

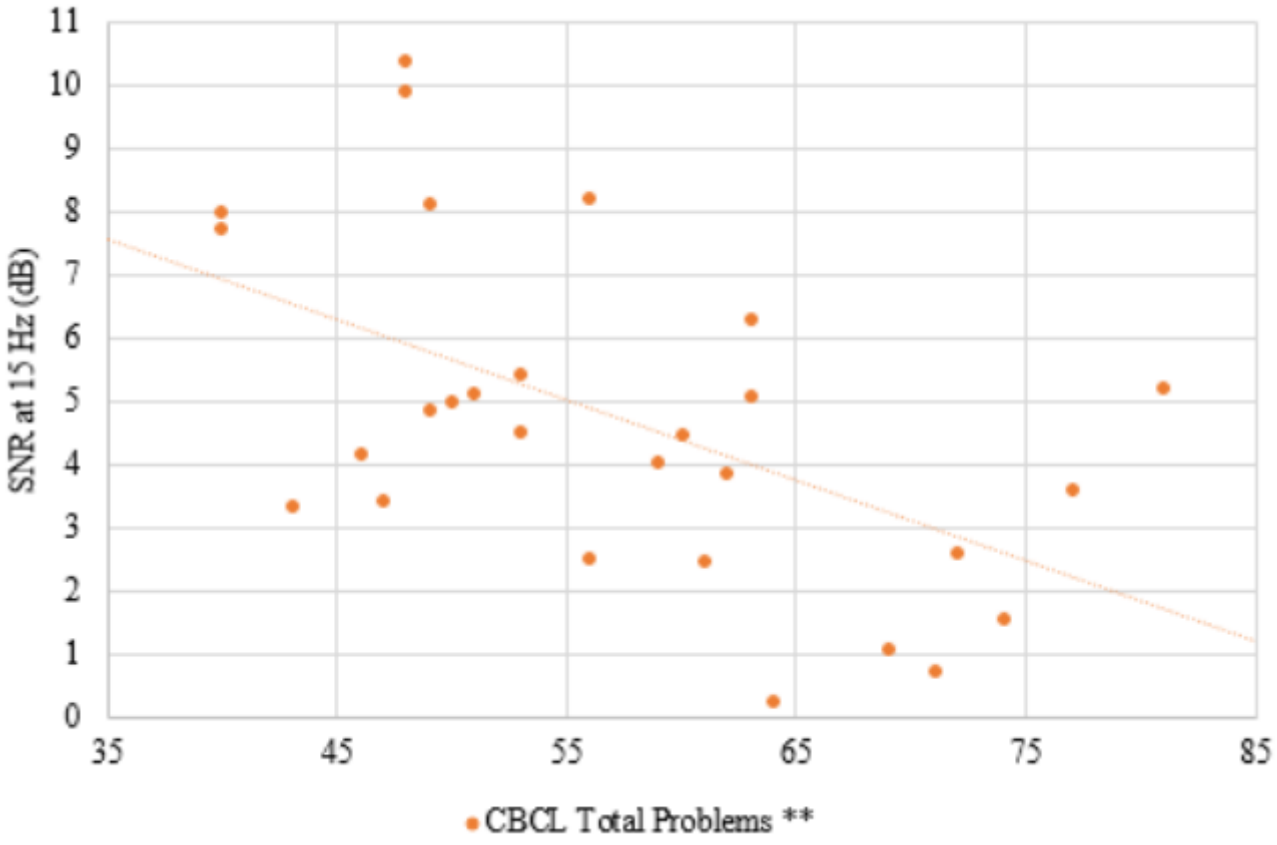

Figure 7

Relationship between the SSVEP SNR at 15 Hz and the CBCL Total problems scale in the NF1 group. **p < 0.01.

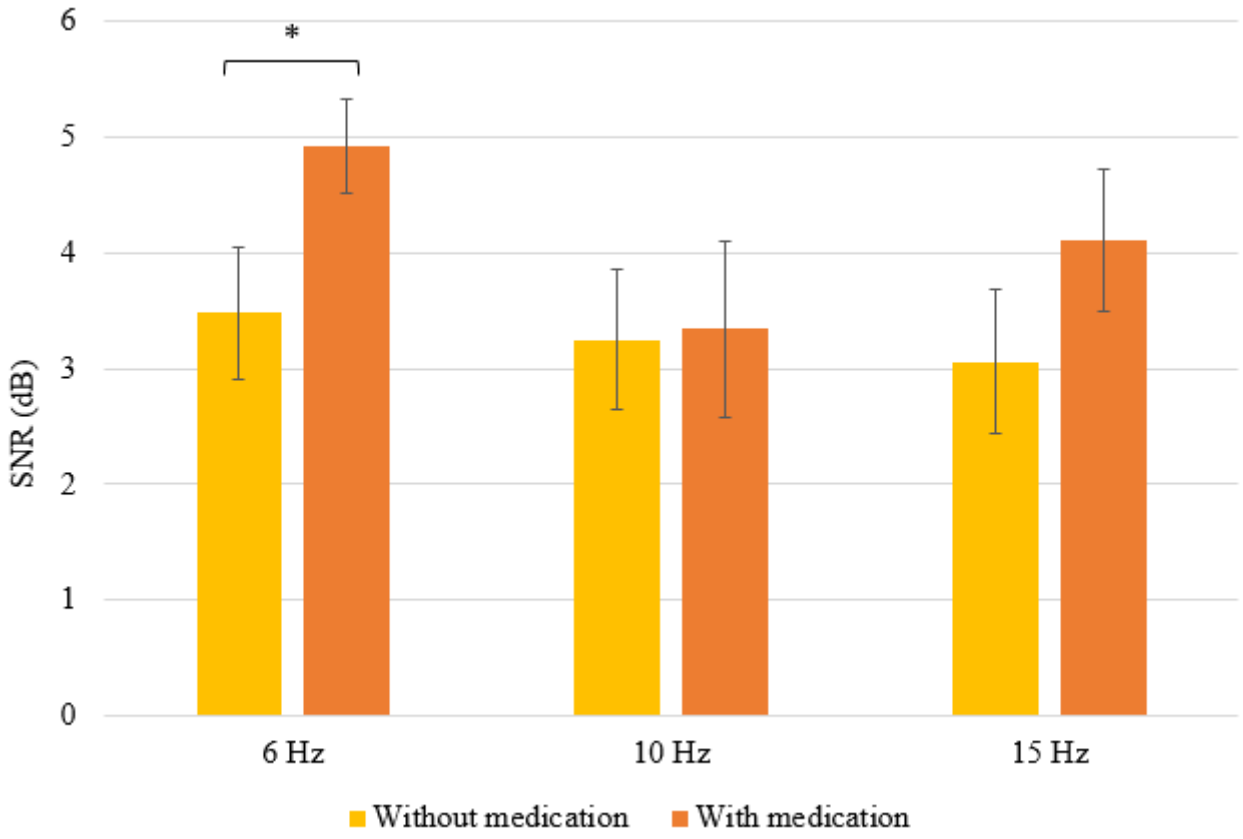

Figure 8

Mean SSVEP SNRs (with standard errors as error bars) in children with NF1 without and with psychostimulant medication (N=8) at each stimulation frequency. *p < 0.05.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1.docx
- Additionalfile2.docx