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Research Article

Impairment of Procedural Learning and Motor Intracortical Inhibition in Neurofibromatosis Type 1 Patients

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ABSTRACT

Background: Cognitive difficulties are the most common neurological complications in neurofibromatosis type 1 (NF1) patients. Recent animal models proposed increased GABA-mediated inhibition as one underlying mechanism directly affecting the induction of long-term potentiation (LTP) and learning. In most adult NF1 patients, apparent cognitive and attentional deficits, tumors affecting the nervous system and other confounding factors for neuroscientific studies are difficult to control for. Here we used a highly specific group of adult NF1 patients without cognitive or nervous system impairments. Such selected NF1 patients allowed us to address the following open questions: Is the learning process of acquiring a challenging motor skill impaired in NF1 patients? And is such an impairment in relation to differences in intracortical inhibition?
Methods: We used an established non-invasive, double-pulse transcranial magnetic stimulation (dp-TMS) paradigm to assess practice-related modulation of intracortical inhibition, possibly mediated by gamma-minobutyric acid (GABA)ergic-neurotransmission. This was done during an extended learning paradigm in a group of NF1 patients without any neuropsychological deficits, functioning normally in daily life and compared them to healthy age-matched controls.
Findings: NF1 patients experienced substantial decline in motor skill acquisition ($F = 9.2$, $p = 0.008$) over five-consecutives training days mediated through a selective reduction in the early acquisition (online) and the consolidation (offline) phase. Furthermore, there was a consistent decrease in task-related intracortical inhibition as a function of the magnitude of learning ($T = 2.8$, $p = 0.014$), especially evident after the early acquisition phase.
Interpretations: Collectively, the present results provide evidence that learning of a motor skill is impaired even in clinically intact NF1 patients based, at least partially, on a GABAergic-cortical dysfunctioning as suggested in previous animal work.
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1. Introduction

Alterations in the balance of excitatory-inhibitory neurotransmission might underlie the cognitive and learning deficits found in several neurodevelopmental conditions (Ramamoorthi and Lin, 2011). Neurofibromatosis type 1 (NF1) is a common single gene disease affecting the human nervous system, inherited in autosomal dominant manner (Friedman and Birch, 1997). Besides cutaneous and musculoskeletal manifestations, cognitive problems resulting in learning disabilities are the most challenging complication, impacting the quality of life of the affected individuals (Krab et al., 2008). In addition, NF1 patients exhibit motor skill impairments. Johnson and colleagues investigated motor proficiency in NF1 children ($n = 26$, age = 4–15 years) using the Bruininks-Oseretsky Test (BOT 2) instrument. Patients presented significant impairments in a composite score including fine manual control, manual coordination, body coordination, strength and agility (Johnson et al., 2010). In a complementary study, Feldmann and colleagues showed in their cohort, which also covered adult NF1 patients ($n = 100$, age = 6–37 years), impaired fine motor skills. Furthermore, patients with focal areas of high signal intensity on T2-weighted MRI scored worse in cognitive and fine motor performance (Feldmann et al., 2003).

Until now, little is known whether NF1-adults without cognitive and attention deficits experience difficulties in learning abilities, such as acquiring a new skill. The interest of this study was to detect possible deficits, which usually go under the radar of standard assessments.

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Whereas, in most adult NF1-patients cognitive and attentional deficits, as well as tumors might be contributing confounding factors.

NF1 occurs by mutation of the *Nf1*-gene that encodes the Neurofibromin-protein, a negative regulator of the RAS signaling cascade. Animal studies have revealed that the Neurofibromin-protein modulates gamma-Aminobutyric acid(GABA)ergic neurotransmission leading to enhanced inhibitory activity directly affecting the induction of long-term potentiation (LTP) and learning (Costa et al., 2002). Recent studies using magnetic resonance spectroscopy measured the levels of GABA and glutamate + glutamine in the medial frontal cortex and the occipital cortex in NF1 patients. The GABA levels in patients were reduced in the medial frontal and occipital cortex when compared to controls. The glutamate + glutamine levels were normal, pointing to an abnormal inhibition/excitation balance in NF1. The medial frontal GABA levels correlates with intellectual abilities and inhibitory control. Interestingly, NF1 patients presented a reversed pattern, with higher GABA being associated with faster responses (Ribeiro et al., 2015). In this context, recent evidence supports the view that modulation of tonic GABA is essential for LTP-like plastic changes e.g., within the motor cortex (M1), (Stagg et al., 2011; Floyer-Lea et al., 2006) and further pharmacological studies demonstrated that GABA-agonist medication might suppress M1 plasticity and learning in healthy individuals (Butefisch et al., 2000).

In the present study, we investigated a well-defined and selected group of NF1 patients fully active in daily life, with normal intelligence and without motor or cognitive impairments carrying the NF1 mutation and compared them to age-matched controls. Participants were investigated over an extended course while learning a novel and challenging motor skill. In addition, by applying a well-established double-pulse transcranial magnetic stimulation (dp-TMS) protocol, intracortical (GABAergic) inhibition in the contralateral M1 was non-invasively assessed (Ziemann et al., 1996; Mainberger et al., 2013), during resting and movement-related states, to determine underlying pathophysiological mechanisms (Heise et al., 2013; Hummel et al., 2009; Liuzzi et al., 2014). We hypothesized, that NF1 patients show an impairment in motor skill acquisition, and that these deficits will be paralleled by impaired modulation of inhibitory neurotransmission in the M1.

2. Methods

2.1. Subjects

NF1 patients (aged 35·8 ± 11·0SD, range 25–58 years, 5 female) were carefully selected from a database of 1·200 NF1 patients. Out of the database, a selection was made according to local eligibility (metropolitan area of Hamburg, Germany). Based on this procedure, approximately 200 patients were determined. 35 patients were then identified according to the inclusion and exclusion criteria, of which 9 agreed to be enrolled in the study. All patients were genetically tested; in seven out of the 9 patients the diagnosis was genetically confirmed (see supplementary Table 1). Additionally, nine healthy subjects (aged 30·11 ± 13·2SD, range 24–65 years, 6 female) were included as a control group. Participants were assessed to be right handed by the Edinburgh handedness inventory (Oldfield, 1971), none of them had reported any history of serious neurological or psychiatric diseases or any contraindications for TMS, as probed by standardized questionnaire (Rossi et al., 2009). NF1 patients were included based on the following criteria: (1) absence of any cognitive impairments determined by a detailed neuropsychological testing including the mini–mental state examination (MMSE), and the German version of Wechsler adult intelligence scale (WAIS-III) (see Table 1). The patients showed no abnormalities in the test of variables of attention (TOVA), the Wender Utah rating scale (WURS-k), the ADHD self rating scale (ADHS-SB), and the hospital anxiety and depression scale (HADS) (see Table 1), (2) absence of visual impairment or any musculoskeletal dysfunction compromising normal finger movements, (3) normal neurological examination and normal clinical MRI, and (4) fulfilling the NIH clinical diagnostic criteria for NF1 (Gutmann et al., 1997). The 5–15 [FTF] was performed in the NF1 patients. The FTF is an established, free and validated questionnaire, covering development and behavior of children in ages 5 to 15 years (Korkman et al., 2004; Trillingsgaard et al., 2004). In regards to our purpose; we used only the motor skill development part (points 1–17) of the questionnaire. Furthermore, none of the participants took any CNS active medication during the course of the study. Besides age, healthy controls were also matched for the educational level. Participants were naïve to the experimental purpose and none of them were professional piano players or trained typists. Local institutional ethics committee approved the study and participants gave their written informed consent according to the ethical declaration of Helsinki (http://www.wma.net/en/30publications).

2.2. Motor Task and Study Design

Skill learning was tested using an adapted version of the sequential finger-tapping task (Zimerman et al., 2013). Participants had to repeatedly tap the explicitly provided sequence on a four-button electronic keyboard with their non-dominant hand. They were instructed to tap as precisely and quickly as possible, according to the written instruction. During the study, subjects were comfortably seated in front of a 20-in. screen; all sessions were performed at the same time of the day in each participant. Before training, participants were first familiarized with the task and then performed a warm-up block. The training period consisted of five sessions divided in 5 consecutive days (20 min each). Motor performance was re-tested after 20 days of the initial training (long-term retention). A personal computer with Presentation (Neurobehavioural System, Albany, USA) was used to present the

Table 1
Characteristics of NF1 patients. M = male; F = female; MMSE = mini–mental state examination; IQ = intelligence quotient (mean = 100, SD = 15), measured with the German version of Wechsler Adult Intelligence Scale (WAIS-III). TOVA = Test of Variables of Attention, RTV = response time variability, RT = response time (mean = 100, SD = 15); WURS-k = Wender Utah rating scale, short-version for the assessment of the attention-deficit hyperactivity disorder in childhood (cut-off ≥30); ADHS-SB = ADHD Self Rating Scale (cut-off ≥15); HADS = Hospital Anxiety and Depression Scale (cut-off ≥8).

NF1 Patients	Age	Gender	Profession	MMSE	Full IQ	Verbal IQ	Performance IQ	TOVA RTV/RT	WURS-k	HADS-D anxiety	HADS-D depression	ADHS-SB
NF1-01	36	F	Teacher	30/30	108	108	108	109/115	4	6	1	10
NF1-02	32	M	Architect	30/30	132	138	118	113/119	4	2	4	7
NF1-03	40	F	Baker instructor	30/30	95	92	101	118/126	13	4	2	8
NF1-04	20	M	Student	30/30	113	120	102	93/119	7	0	4	8
NF1-05	25	F	Teacher	Missing[a]	102	102	104	112/131	2	6	2	4
NF1-06	44	F	Nurse	30/30	127	121	127	119/123	2	6	2	6
NF1-07	58	M	Fireman	30/30	111	112	108	124/157	6	3	2	7
NF1-08	35	F	Tax-consultant	30/30	92	91	93	102/112	3	7	7	6
NF1-09	33	M	Graphic designer	30/30	92	96	89	107/115	21	6	3	13
Mean +/− SD	35,8 +/− 11			30/30								

All participants presented normal or above normal IQ. None of the NF1 participants exhibit attention deficits, depression or anxiety.
[a] One patient refused to do the MMSE.

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