Selective impairment of the executive attentional network in adult patients with neurofibromatosis type 1

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Introduction

Neurofibromatosis type 1 (NF1) is a rare orphan autosomal dominant inherited disease with an incidence rate of approximately 1/3000 [1]. The prominent physical symptoms of NF1, such as café au lait spots, axillary freckling, Lisch nodules, osseous lesions and benign/malignant neural tumours, are well documented. Only approximately 20% of NF1 cases include significant physical complications [2]. Meanwhile, abnormalities of structures

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networks, including the ability to maintain alertness, the ability to orient the sensory input and perform control functions [13]. Identification of the general or selective impairments in attention in adult patients with NF1 would enable us to understand higher-level functional deficits in this population. This study sought to determine whether adult patients with NF1 have attentional impairment and, if so, to clarify the profile of attention deficits in these patients by isolating the particular aspect of attentional processing that is responsible. Based on previous research in children, we predicted that adult NF1 patients would show deficits in performance on different aspects of the attention task. The study will clarify the precise characteristics of attentional precisely in adult NF1 patients.

Methods

Participants

Twenty-six NF1 adult patients with NF1 and 20 neurologically intact normal controls (NCs) participated in the study. Four NF1 patients were excluded because they did not complete the task, and two patients were excluded owing to severe depression as measured by the Beck Depression Inventory (the BDI scores of those two patients were 33 and 30 out of 39, respectively). The final sample included 20 adult NF1 patients and 20 NCs (see Table 1 for demographic information of the final samples). All participants were right-handed, had normal or corrected-to-normal vision, and reported no previous or current psychiatric conditions. All participants underwent the same experimental procedures, and they were informed of the study requirements and gave written consent before participation. The study was approved by the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University, China.

All participants completed the Mini-Mental State Examination (MMSE) and the short form of the BDI (BDI-SF). The MMSE is commonly used in clinical settings to screen for cognitive impairment [14]. This instrument includes 11 items that assess eight categories of cognition: orientation to time, orientation to place, registration, attention and calculation, recall, language, repetition and complex commands. The maximum possible score is 30 points. Any score greater than or equal to 25 points indicates normal cognition. Scores below this threshold indicate severe (≤9 points), moderate (10–20 points) or mild (21–24 points) cognitive impairment. We used the 13-item BDI-SF to assess the general emotional state of each participant [15]. The BDI-SF is appropriate for screening depressive symptoms in medical patients and has been shown to have good internal consistency [16]. The 13 items include sadness, pessimism, feeling of failure, lack of satisfaction, feeling of guilt, self-disgust, suicide, social withdrawal, indecisiveness and a sense of unattractiveness. All patients were free of apparent cognitive impairment as measured by the MMSE and had slightly high scores (indicating depressive mood symptoms) on the baseline administration of the BDI-SF (Table 1). The NF1 and NC groups were matched for age ($t_{(38)}$ = −1.32, P = 0.19), educational attainment ($t_{(38)}$ = -1.64, P = 0.11), BDI scores ($t_{(38)}$ = 1.56, P = 0.13) and MMSE scores ($t_{(38)}$ = 1.23, P = 0.23). Most of the patients suffered cutaneous disturbances but no self-reported cognitive problems in daily life, and two of these patients complained of slight memory decline.

The revised attention network test

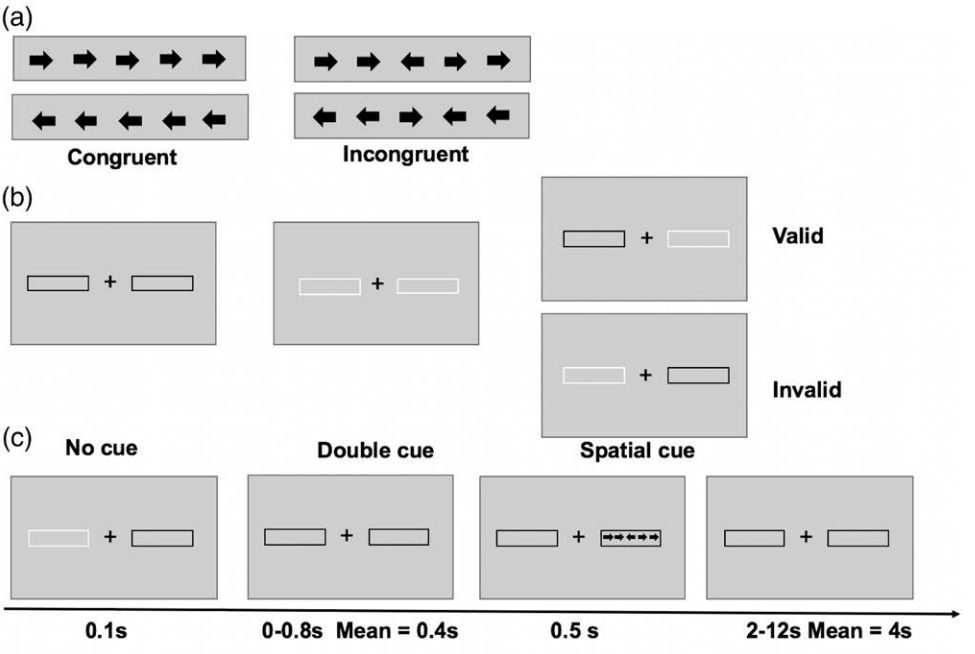
The revised attention network test (ANT-R) was used to examine the efficiency of each of the three independent attentional networks: the alerting, orienting and executive control networks [17]. Participants were required to identify as quickly and accurate as possible the direction of a centrally presented arrow that was flanked on the right and left by two arrows. The flankers could point either in the same direction as the central target arrow (congruent) or in the opposite direction (incongruent) (Fig. 1a). The function of the executive control network was defined by the conflict effect, that is, the performance difference between the incongruent and congruent conditions. In each trial, either a 100-ms visual cue (brightening the box) or no cue was presented 0, 400 or 800 ms before the target display. Four types of cues were used (Fig. 1b): (1) no cue (neither box was brightened before the target display); (2) a double cue (both boxes were brightened); (3) a valid cue (one of the boxes was brightened, always cuing the correct location of the target display); and (4) an invalid cue (one of the boxes was brightened, always predicting the location opposite to the target display). The function of the alerting network was measured by the alerting effect, that is, the performance difference between the double-cue and no-cue conditions. The function of the orienting network was measured by the validity effect, that is, the performance difference between the invalid-cue and valid-cue conditions. The experiment consisted of four blocks, with

Table 1 Demographic and clinical characteristics

	Age (years), mean (95% CI)	Sex	Education (years), mean (95% CI)	MMSE, mean (95% CI)	BDI, mean (95% CI)
NF1	29.5 (3.7)	8 male	10.6 (1.6)	28.9 (1.0)	9.5 (2.5)
NC	33.1 (3.9)	8 male	12 (1.3)	28.3 (1.1)	7.0 (2.6)
P value	0.504	1.000	0.109	0.226	0.132

Age, the age at the experiment; BDI, the score of the Beck Depression Inventory-short form; CI, confidence interval; MMSE, Mini-Mental State Examination: a measure of global cognitive impairment; NC, neurologically normal control; NF1, neurofibromatosis type 1.

Fig. 1



Illu- a i f f he evi ed a ef i f fe k e (ANT-R). (a) Flafke e . The cef al a ge a if ed he ame di ec i f a he afke ffde he c fg ffef c fdii f, hile if ifg he ie di ec i f ffde he if c fg ffef c fdii f. (b) Cffe e . F f c ffe c fdii f, fei he b a b igh ef ed. F d ble cffe c fdii f, b h b e e e b igh ef ed. F a ial c fdii f, a valid cffe b igh ef ed he b al a cffifg he c ec l cai f he a ge di la , hile af if valid cffe b igh ef ed he b al a edic ifg he l cai f ie he a ge di la . (c) The ial ffe e f he a k. A cffe (0.1 ec fd) a f ll ed b a va iable a i f di la (0 0.8 ec fd), afd hef b he a ge di la (0.5 ec fd) afd a va iable if e - ial if e val (2 12 ec fd).

72 trials in each block. The total time required to complete the task is approximately 30 minutes, which is suitable for studies of patients. The experimental program was presented in E-prime (Psychology Software Tools, Pittsburgh, Pennsylvania, USA). Participants' reaction time (RT) and accuracy were recorded.

Data analysis

The effects of the attentional networks in ANT-R were compared between the NF1 group and the HC group to reveal the networks might be functioning abnormal in NF1 patients. The scores of each of the three networks in ANT-R were calculated according to the previous study [17]. Incorrect responses were excluded from the computation of the mean RTs. The effects in RT and accuracy were entered into repeated-measures analysis of variances (ANOVAs), with attentional network (alerting, orienting or executive control) as the within-subject factor and group (NF1 and NC group) as the between-subject factor. In addition, we calculated Bayes factors (BFs) with a Cauchy prior distribution to determine the relative strength of evidence for the null and alternative hypotheses [18]. A BF smaller than 1/3 indicates substantial evidence for the null hypothesis. The BFs were calculated using JASP [19].

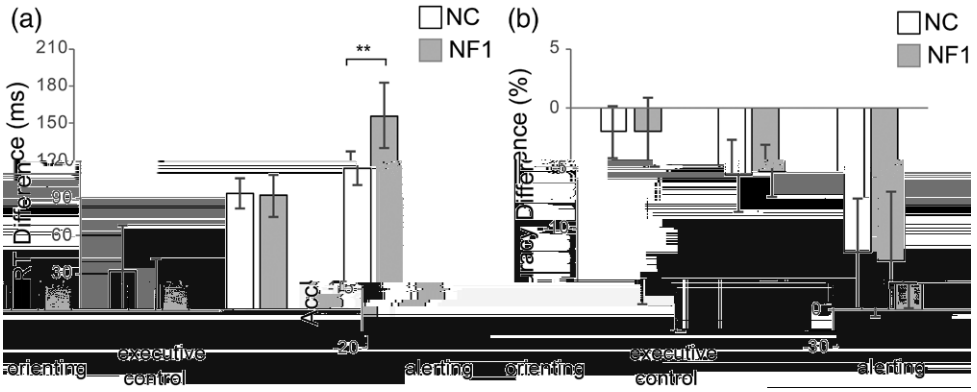
Results

Selective deficit in the executive control network in adult NF1 patients

The overall mean RTs of the NC and NF1 groups were 642 ± 28 ms (mean ± SD) and 700 ± 42 ms, respectively, and their accuracy rates were 91.65% ± 3.02% and 87.43% ± 3.00%, respectively. Independent *t*-tests showed that the NF1 group was significantly slower ($t_{(38)} = 2.25$, $P = 0.03$, BF = 2.15) and marginally less accurate ($t_{(38)} = -1.97$, $P = 0.06$, BF = 1.23) than the NC group.

Repeated-measures ANOVA on RT revealed a significant interaction between attention network (alerting, orienting or executive control) and group (NF1 or NC) ($F_{(2,76)} = 5.02$, $P = 0.009$, BF = 10.21) (Fig. 2a), but no such interaction was found for accuracy ($F_{(2,76)} < 1$, BF = 0.11) (Fig. 2b). Planned simple comparisons revealed that the executive control network showed a significant effect of group ($F_{(1,38)} = 8.07$, $P = 0.007$, BF = 6.39), such that NF1 patients demonstrated greater conflict effect (156 ± 26 ms) compared to the NC group (114 ± 13 ms), while the differences between groups in alerting or the orienting network were NS (alerting: $F_{(1,38)} < 1$, BF = 0.39; orienting: $F_{(1,38)} < 1$, BF = 0.32). These results suggest that there was the selective deficit in executive control

Fig. 2



Behavi al e l f he ANT-R. NF1 a ie h ed elec ive de ci ie e ec ive c l e k, b e evide ce f de ci ie ale ie g ie ie g f c i . Re l e eac i ime diffe e ce (a) a d acc ac diffe e ce (b). ANT-R, evi ed a e i e e k e ; NF1, e b ma i e 1.

of attention in adult NF1 patients, but no evidence of deficits in alerting and orienting functions.

Clinical assessment results

The NF1 patients fulfilled the diagnostic criteria as specified by the NIH Consensus Development Conference [20]. All patients had small benign subcutaneous nodules or café au lait spots on the trunk and extremities; these skin features did not affect normal activities. The patients were in stable clinical situation and could go about their work and daily activities independently. The patients had not undergone surgery and had no serious diseases that affected their quality of life (such as scoliosis and other osseous lesions). All patients had normal MMSE scores (score 28.9 ± 0.7, out of 30, Table 1), while their BDI scores showed moderate depressive symptoms (score 9.8 ± 2.9). None of the patients showed any dysfunction on routine neurological examination.

Discussion

Inefficiency of execution control of attention in patients with NF

Attention and attentional functions (i.e. the alerting, orienting, and executive control functions) are supported by independent and integrative brain networks [13]. The ANT-R tests these three functions of the attention network in a single task, making it possible to use one test to simultaneously evaluate the three functions of the attention network and to study the interaction of the three subnetworks [17]. However, there has been controversy about the efficiency of these three networks acting on human attention and the interactions between them. The previous literature on attention deficits in NF1 patients (mostly focussed on children) does not explicitly show which specific domain of attention has abnormal function. In the current study, the ANT-R results showed that there was a significant decrease only in the executive control function of NF1 patients, mainly due to the prolonged RT (flanker effect) under conflict conditions. At the same time, there was no evidence found for abnormalities in the alerting or orienting attentional function in adult NF1 patients. The executive dysfunction dissociated from the alerting and orienting functions supports the notion that these three attentional networks are separable and relatively independent.

In a previous study, up to 70% of child patients with NF1 had defects in one or more aspects of the attention system (sustainability, selectivity, dispersion and distraction). Visual-spatial dysfunction is considered a ‘characteristic’ phenotype of NF1 patients. Children with NF1 have been shown to have serious defects in visual-spatial learning ability. In addition, children with NF1 have a slow response to visual signals, long RT and weak resistance to interference, resulting in unstable attention [21]. This finding suggests that NF1 patients face obstacles throughout the processing of visual information. However, slowed or impaired ability to shift visual attention towards cued locations was not found in the current study, indicating that NF1 patients maintain adaptive allocation of visual attention. Some prior studies have proposed that executive deficits are strongly correlated with intelligence quotient (IQ) in children with NF1. This hypothesis is inconsistent with the current data. Although we did not collect the IQs of the NF1 group, most of the participants showed average academic achievement, and none of the NF1 patients had self-reported or MMSE-identified cognitive impairments. Consistent with previous findings in children with NF1 and older adults, the executive control deficits of adult NF1 patients may result from the impairment of frontoparietal circuits. It is worth noting that inhibition and cognitive flexibility are essential to process the conflicting information in the ANT-R; one possibility is that the

deficit in behavioural inhibition results in executive deficits that depend on this inhibition.

Cognitive impairment is an important characteristic in patients with neurofibromatosis type 1

Cognitive deficits in children with NF1 were first identified as a problem due to poor academic performance. Some children with NF1 also showed deficits on intelligence tests, and their scores were significantly lower than those of healthy children of the same age. Most children with NF1, even if their mental development is fundamentally normal, have complex cognitive impairments affecting perception, executive function and language skills; these impairments cause learning difficulties, which constitute the main symptom of NF1. At the same time, 40% of children with NF1 show ADHD-like performance deficits [22], such as executive control disorder, planning choice ability defects and learning defects, which seriously affecting their ability to develop and pursue an education. In addition, increasingly many studies have noted that various types of cognitive damage last throughout the lifespan. For adolescents with NF1, symptoms such as impaired motor development, visual-spatial judgment and visual-motor integration suggest that NF1 may affect multiple stages of cognitive processing [12]. In an overall cognitive assessment of elderly patients with NF1, a mild intelligence deficit was found, and short-term memory showed a significant decline, confirming that cognitive dysfunction is persistent and evolving in the progression of NF1 [10]. Generally, the cognitive impairments caused by NF1 are multidimensional phenomena that involve several psychological processes, moreover, all of these processes are related to executive control of attention which is the key process associated with the NF1's decline in cognitive abilities.

Potential neural mechanism underlying cognitive dysfunction in neurofibromatosis type 1

Cognitive processing by the brain is based on a complex neural network involving multilevel regulatory mechanisms. The mechanisms that cause NF1-associated cognitive impairment include molecular and cellular signalling pathways, neuronal differentiation and many other complex factors [9], the most important of which are the roles of neurotransmitters and neuronal activity.

Abnormalities in local brain activation and structure of the whole brain network

In recent studies of brain functional status and structures using new neuroimaging techniques, NF1 patients demonstrated enhanced connectivity of the default-mode network [8] and abnormal activation of the visual cortex of the brain [23], along with reduction of the fractional anisotropy of the regional fibre bundles in the thalamus and basal ganglia [5] as well as decreased grey matter volume in the superior temporal gyrus [6]. These results suggest that NF1 leads to both functional and structural alterations that might underlie the accompanying cognitive deficits. On the one hand, the genetic mutation associated with NF1 has a potential impact on the molecular and cellular structure of the brain, which is an important cause of cognitive impairment. On the other hand, to adapt to the changes in abnormal cognitive processing, neural activity and neuronal will reform to be efficient and suitable for the current state through various plasticity mechanisms. Accordingly, we proposed that there are at least two modes of brain functional remodelling associated with NF1: one is the local activity change in specific 'key regions' based on functional separation theory, leading directly to regional cortical remodelling. The other is the reorganization of the whole brain networks based on the functional integration perspective, that is, the coordination of information processing through more sophisticated and comprehensive restructuring within the cognitive control networks.

Imbalanced dopamine system

Dopamine (DA) is one of the most important neurotransmitters to maintain and promote a variety of basic physiological states (such as blood pressure) and complex conscious functions (such as emotions). Importantly, DA is the critical neurotransmitter for attention control during normal physiological activities, and some key nodes of cognitive control networks (i.e. basal ganglia, insula) are also DA-enriched brain regions. Research on animal models of NF1 has provided us with an opportunity to learn more about the pathogenesis of NF1. Previous studies demonstrated that in the striatum of NF1 knockout mice with non-selective and selective attention impairment, post-synaptic DA levels are reduced, whereas the axons of the dopaminergic neurons are shortened. Moreover, such deficits were normalized following either methylphenidate or levodopa administration, emphasizing that the attention abnormality is the consequence of reduced DA levels in the striatum [24]. Combined with behavioural deficiencies such as learning and memory deficits in NF1 mice [25], it is currently speculated that imbalances in the DA system are important factors that cause NF1 cognitive abnormalities [9].

The significance of cognitive assessment of neurofibromatosis type 1

Characterizing the underlying neural mechanism of cognitive processes is crucial for elucidating brain functions and diagnosing and treating brain diseases. Although animal research can help to understand some of the mechanisms of neural activity, due to human-specific advancements in intelligence, the results of animal studies are still distant from the reality of human beings. The complexity of the human brain itself and the limitations of research methods have constrained the further exploration of cognitive activities in the brain. The

relatively clear genetic background of NF1-related cognitive impairment provides an opportunity to analyse the neurophysiological basis of complex cognitive activities. The combination of single gene mutations and cognitive impairment makes NF1 a unique model for studying cognitive processing. Increasing numbers of researchers have explored the brain characteristics associated with NF1 cognitive impairment, which provides a new perspective for clarifying the developmental dynamics and the factors influencing cognition.

Taking cognitive impairments as a breakthrough, further research on the inherent neural dysfunctions of NF1 by selective tasks combined with neuroimaging would provide irreplaceable causal evidence for clarifying the neurophysiological basis of complex cognitive processing. These investigations will help us to uncover the pathogenesis of NF1, improve the understanding of NF1 cognitive impairment comprehensively, guide the diagnosis and treatment of NF1, and help to overcome quandaries in the treatment of such complex diseases. Furthermore, given the close relationship between distinct genetic characteristics of NF1 and cognitive impairment, the combined research in cognitive neuroscience and molecular biology will explain the neural mechanisms underlying a series of complex cognitive deficits and provide evidence for the study of other diseases featuring comparable cognitive impairment.

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Conflicts of interest

There are no conflicts of interest.

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