各論—小児期から成人期への臨床経過とその経年的なマネージメント—
精神疾患

チック障害

金生由紀子

Tic disorders

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Abstract

Chronic tic disorders including Tourette syndrome are defined as disorders with tics continuing for over a year. Although a substantial portion of patients with chronic tic disorders have improvement or remission of their tics until adulthood, some of them still have necessity to receive treatment for tic disorders in adulthood. Regardless of age and severity of tics, basic treatment for tic disorders consists of psycho-education and family guidance which encourage patients and people around them to understand, accept and cope with tics appropriately. In most of the adult cases with tic disorders who require aggressive treatment, tics and/or comorbidities including obsessive-compulsive symptoms are so severe that they usually have medication including antipsychotics.

Key words: tic disorders, Tourette's disorder, obsessive-compulsive disorder, comorbidity, adult

はじめに

チックは幼児期の後半から児童期に生じやすく子どもの10-20％が経験するというが，多くの場合で持続期間が1年未満である．持続期間が1年以上の慢性チック障害であっても，成人までにはチックが軽快・消失していることが多い．それにもかかわらず成人期にも引き続いてチック障害の治療を要する場合が一定数存在することも事実である．チックの基本的な特徴を踏まえたうえで，成人期への移行について検討したい．

1. チックの定義と特徴

チックは，突発的，急速，反復性，非律動性，常同的な運動あるいは発声であると定義されている．一般的に抵抗できないものと感じられるが，ある程度の時間であれば制御でき，その時間は様々である．不随意運動とされてきたが，このように部分的でも随意的抑制が可能であることから，‘半随意’と考えられるようになっている[1]．

運動チックと音声チックは，それぞれが素早い典型的な単純チックとややゆっくりで目的性があるようにみえる複雑チックに分けられる．単純運動チックは最もよく認められ，そのなか

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でも瞬きなどの目のチックが最も多い．複雑運動チックは体のいろいろな部分が一緒に動くチックである．単純音声チックでは，咳払いが最も多い．複雑音声チックでは，状況に合わない単語や句の繰り返しが一般的である．

チックにはやらずにはいられないという抵抗しがたい感覚を伴い，チックをするとすっきりしたりほっとしたりして，この感覚が軽快・消失することが少なくない．この感覚は，前駆衝動(premonitory urges)または感覚チック(sensory tics)と呼ばれる[2]．

チックは心理的な影響で変動することが多い．不安や緊張が増大していくとき，強い緊張が解けたとき，楽しくて興奮したときなどに増加しやすい．一方，一定の緊張度で安定しているとき，集中して作業をしているときなどに減少する傾向がある．心理的な理由だけでなく，疲労で増加したり発熱で減少することがある．更に，自然に変動することもしばしばある．

2. チック障害の分類

チックを主症状とする症候群がチック障害である．18歳以下で発症して4週間以上持続するチック障害は，チックの特徴と持続期間から，一過性チック障害，慢性運動性あるいは音声チック障害，Tourette症候群(Tourette syndrome: TS)の3つに分けられる．持続期間が1年以上の場合が慢性とされる．なお，TSについては，Gilles de la Touretteの報告でエコラリア(echolalia，反響言語：ほかの人の言った言葉などの繰り返し)およびコプロラリア(coprolalia，汚言症：社会に受け入れられない，しばしば卑猥な単語を言ってしまうこと)という複雑音声チックが重要な特徴とされたが，それらは現在では診断に必須ではない．

3. チック障害の併発症

チック障害，とりわけTSには様々な精神神経障害を併発する．以下ではTSを中心に述べるが，慢性チック障害にほぼ共通すると思われる．

a. 強迫性障害(obsessive-compulsive disorder: OCD)および強迫症状

チック障害とOCDや強迫症状とには密接な関連がある．特にTSでは約30％がOCDを併発する．

OCDや強迫症状を伴うTSでは，TS単独と比べて，チックの発症時から複雑運動チックを認める率が高く，チックの発症年齢がやや高く，チックがより重症であるとされる．自傷行為がより高率になるともいう．OCD以外の精神科的併発症の数が多くなるともいう．

また，典型的なOCDでは強迫観念が起こって不安になるのでそれを打ち消そうと強迫行為を行うのに対して，TSとOCDの併発ではこのような不安はあまりなく，強迫行為は自動的に起こる傾向があるとされる．TSにおける強迫症状は，‘まさにぴったり(just right)’にせずにはいられないという知覚に伴って起こるチック様強迫症状であり[3]，衝動性の統制の悪さで特徴づけられていると思われる．

b. 注意欠陥/多動性障害(attention-deficit/hyperactivity disorder: AD/HD)

AD/HDはOCDと並んでTSに併発する頻度が高く，50％以上に及ぶとの報告すらある．一方，AD/HDにはチックを伴いやすい傾向もあり，チックの頻度はAD/HDの成人(12％)で一般の成人(4％)よりも高いとの報告がある[4]．ただし，TSとAD/HDとの併発例と思われている一部にはチックのためにAD/HD症状を呈している者がいるのではとの指摘もある[5]．TSにAD/HDを伴うと，チックそのものが重症になるとはいえないが，衝動性や攻撃性がかなり増加し，社会適応も障害される[6]．

c. その他

生活に支障をきたす併発症状としては，‘怒り発作(rage attack)’もある．‘怒り発作’とは，状況に比べとても過度または不適切にひどく腹を立ててコントロールできなくなることである．元来の性格には似つかわしくない行動であり，まさに‘きれる’という表現がぴったりである．‘怒り発作’と不安やうつとの関連が示唆されており，治療上は自己評価の低下に配慮が要るだ

ろう[7].

不安やうつの傾向はTSで健常対照よりも高いとの報告もある[8]. 精神科を受診するTSでは不登校を呈することもしばしばある.

また, TSに広汎性発達障害(pervasive developmental disorders: PDD)を併発することもあり, その頻度は1-9%と報告されている. 一方, PDDにTSを伴う頻度は2.6-50%とされており, 調査方法によってかなりの幅があるが, 少なくとも一般人口よりは高頻度といえよう[9]. TSとPDDとの併発は発達水準にかかわらず起こる.

4. チック障害および併発症の経過

a. チックの経過

チックは4-11歳頃に発症することが多く, 6-7歳頃に最もよく認められる. 通常は単純運動チックで発症する. 複雑運動チックや単純音声チックが出現する場合には, これに次いで平均9-10歳頃であることが多い. 更に, コプロラリアなどの複雑音声チックの出現年齢については, 平均11-13歳頃となる. 前駆衝動は10歳頃から報告されるようになり, 14歳以上で頻度が大きく増加する.

TSが運動チックで発症する場合には上記のとおりであることが多いが, 音声チックで発症する場合には運動チックや複雑音声チックへの進展が速かったとの報告もある[10].

TSでも, 10歳から10歳代半ば過ぎくらいを極期としてそれ以降はチックが軽快の方向に向かうことが多い. 90%が成人期の始まりまでに軽快・消失の方向に転じているとされている. ただし, 少数では成人まで重症なチックが続いたり, 成人後に再発したりすることがある. そのような場合には, 人生のうちで最も激しい症状を成人後に体験することがある[11].

b. 併発症の経過

TSに強迫症状を伴う場合は, 10-20歳の間に出現することが多いとされる. TSの追跡研究から, チックが最も重症な年齢の約2年後に強迫症状が最も重症となったとの報告もある[12]. チック障害では思春期頃にOCDや強迫症状が発症しやすいと思われる.

一方, AD/HDはチックに先立って発症していることが多いだろう. AD/HDを伴うと, より早く受診してチック障害とAD/HDの併発と診断されやすいかもしれない.

5. 成人期のチック障害の特徴

先述したように慢性チック障害でも成人までにはチックが軽快していることが多いが, 一部には成人期も治療を要する場合がある. チック自体の特徴はそれまでと変わらないが, 長期の経過に伴って, 本人のチック障害に対する構えの変化, 筋力の増強, 社会の受け入れの問題などのために異なった様相を呈することになる.

自験例では成人チック患者は治療の主な標的に基づいてチックのみ群, チックと併発症群, 併発症のみ群の3群に分けることができた[11]. チックと併発症群ではチックの最悪時に3群中で最もチックが重症で社会適応も最も不良であった. また, 経過中のOCDと自傷行為が最も多かった. 併発症のみ群は評価時にチックが最も軽症になっているのにもかかわらず就労している割合が最低であり, 社会適応上の困難を有していた.

音声チックの方が運動チックよりも社会的機能への影響が大きい[13]のは想像するに難くない. 同時に, 動きが激しくかつ頻回であったり全身に及んだりする運動チックは痛みや疲労を引き起こす可能性がある. チックと強迫行為の境界にあるような症状として, 壊したくないと思うと余計にものを叩いたり投げつけたりしてしまうとか, 傷つけてはいけないと思うと余計に自分の顔面や体を叩いたり壁にぶつかったりしてしまうことが時にあり, 大きな苦痛をもたらす. また, チックがかなり軽快しているように見えても, 前駆衝動によって落ち着けないことが問題になることもある.

6. 成人期を含めたチック障害の治療

a. チック障害の治療の基本

治療にあたっては, ①チック自体の重症度(チックが直接的に生活に支障をきたす度合い), ②チックによる悪影響の重症度(自己評価や社会適応に対するチックの悪影響の度合い), ③

併発症状の重症度(チックと密接に関連して伴いやすい併発症が生活に支障をきたす度合い)の軸から重症度を総合的に評価して，優先順位をつける[14]．また，本人および家族をはじめとする周囲の人々がチックをどのように認識しているのかも把握しておく．

重症度にかかわらず家族ガイダンスや心理教育および環境調整を行う．チックや併発症状があっても本人が発達し適応していくことができるように，本人および家族や教師などの周囲の人々の理解と受容を促して適切な対応のための情報を提供する．この枠組みの中でチックや併発症状が重症であれば薬物療法が検討されるが，最近ではその比重がやや軽くなっているようである．

家族ガイダンスや心理教育では，チックは親の育て方や本人の性格に問題があるために起こるのではないと確認したうえで，チックの変動性や経過の特徴について伝えて，些細な変化で一喜一憂せずに前向きに生活することを勧める．慢性チック障害であっても変動を繰り返しながら極期を経て軽快に転ずることが多く，チックと上手に付き合って思春期を乗り越えることが大切と話す．治療法としては，限界と副作用はあるものの有効な薬物療法が複数あり，症状を軽減できる可能性があることを必ず伝えておく．

薬物療法は主な標的症状がチックか併発症かで大別される[14]．チックに対する薬物の中心は抗精神病薬であり，チックおよびAD/HD症状などの併発症状に対する薬物としてはclonidineがある．併発症状に対する薬物としては抗うつ薬などがある．

アメリカトゥレット協会医療アドバイス委員会がエビデンスの程度を加味してまとめた薬物療法のガイドラインによると，我が国で使用できる薬物のなかで，チックに対して十分にエビデンスのある抗精神病薬は，haloperidol，pimozide，risperidoneであり，チックに対し て幾らかのエビデンスがある抗精神病薬は，fluphenazine，tiaprideであるとされた．最近では，ドパミン以外の神経伝達物質に作用する非定型抗精神病薬が試みられることが増えており，特に，ドパミン系とセロトニン系に作用してしかもドパミン系についてはその活動性の水準に合わせて安定化を図るというaripiprazoleが注目されている．非抗精神病薬の中で幾らかエビデンスがあるとされたclonidoneはα_2ノルアドレナリン受容体作動性薬の降圧薬である．抗精神病薬よりも有効性が低く，効果の出現まで数週間かかることがあるとされるが，抗精神病薬よりも副作用が軽度であること，AD/HD症状に有効であることから使用される．

併発症状の中で薬物の標的となり得るものには，強迫症状，AD/HD症状，情動不安定，‘怒り発作’を含めた攻撃性などがある．強迫症状やOCDに対しては，セロトニン再取り込み阻害薬(SRI)が使用されることがある．選択的SRI(SSRI)単独よりも少量の抗精神病薬を追加して強迫症状が改善することがある．AD/HD症状に対しては，中枢刺激薬が有効でしかもチックに必ずしも悪影響を及ぼさないとの海外の報告があるが，我が国では禁忌である．我が国でも小児のAD/HD治療に使用可能となった選択的なノルアドレナリン再取り込み阻害薬atomoxetineは，チックを増悪させずむしろ幾らか改善させる可能性が示唆されている[15]．

最近，薬物療法の限界と副作用がより意識され，前駆衝動とその基盤にある脳機能への関心が高まるにつれて，チックの随意的抑制を目指した認知行動療法的アプローチが改めて注目されている．そのなかでも，チックをしたくなったときに拮抗する運動を行ってチックを軽減させようとするハビットリバーサル(habit reversal)という方法の報告が蓄積されつつある．

慢性のチック障害をもつ本人や家族が孤立感をもたずに前向きに生活するうえで，患者・家族グループの果たす役割も大きい．

b. 成人期の治療へ

成人期の治療への移行の前提として，それまでに本人や周囲の人々がチック障害について適切に理解して受け入れるようにすることが重要である．小児期に受けた説明から成人までにはチックが必ず消失すると思い込んでしまい，成人後もチックが持続することに怒りや失望など

を示す人がいる．頻度は少ないものの成人後も重症なチックを有する場合があること，比較的重症であると極期が遅くてむしろ成人してから徐々に軽快していく可能性のあることをあらかじめ確認しておく．

こうして治療を行い，成人までにチックや併発症が生活に支障をきたさなくなったら，再燃時の対応について相談をしたうえでひとまず治療終了できよう．

成人期にも治療を継続する必要が認められたら，一つの節目として治療の標的や目標を再確認するとよいだろう．チックが中等度以上で薬物療法を行っていても，安定した状態が続いたら早期に漸減中止を目指す場合もあれば，持続する重症なチックに対して薬物の調整を含めてより積極的な治療を推進しなくてはならない場合もある．特に後者の場合には，大学を含めた教育機関，就労支援機関，職場などとの連携をしばしば要し，精神障害者保健福祉手帳などの制度の活用を検討することもある．更に，強迫症状をはじめとする併発症の問題が大きい場合には，精神医学的アプローチがより重要となる．成人期に担当医を引き継ぐ際にはOCDに詳しい精神科医も一つの候補になるのかもしれない．

おわりに

TSの追跡研究から，小児期にチックが重症であると青年期・成人期にチックが重症になるとの報告もあるが[12]，チックの予後予測はいまだ難しい．どのような場合に成人期も積極的な治療を要するのか，どうしたらその経過を改善できるのか，神経生物学的な観点からの検討を深めると同時に，生涯発達の観点からより幅広い治療や支援の充実を目指す必要があろう．

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ORIGINAL ARTICLE

Prefrontal Dysfunction in Attention-Deficit/Hyperactivity Disorder as Measured by Near-Infrared Spectroscopy

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Abstract Recent developments in near-infrared spectroscopy (NIRS) have enabled non-invasive clarification of brain functions in psychiatric disorders with measurement of hemoglobin concentrations as cerebral blood volume. Twenty medication-naïve children with attention-deficit/hyperactivity disorder (ADHD) and 20 age- and sex-matched healthy control subjects participated in the present study after giving consent. The relative concentrations of oxyhemoglobin (oxy-Hb) were measured with frontal probes every 0.1 s during the Stroop color-word task, using 24-channel NIRS machines. During the Stroop color-word task, the oxy-Hb changes in the control group were significantly larger than that in the ADHD group in the inferior prefrontal cortex, especially in the inferior lateral prefrontal cortex bilaterally. The Stroop color-word task used with NIRS may be one useful measurement to assess prefrontal brain dysfunction in ADHD children.

Keywords Near-infrared spectroscopy · Attention-deficit/hyperactivity disorder · Stroop color-word task · Prefrontal dysfunction

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a central nervous system (CNS) disorder estimated to occur in 3–7% of school-age children [1]. Functional brain abnormality has been reported in ADHD patients. A mean regional I-123 IMP single photon emission computed tomography (SPECT) region of interest (ROI) count ratios (left to right) study demonstrated that the ADHD patients had greater overall hemispheric I-123 IMP uptake

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asymmetry, with less activity in the left frontal and left parietal regions, in comparison with control patients [2]. Bush et al. [3] also reported anterior cingulate cortex dysfunction in ADHD using the counting Stroop during functional magnetic resonance imaging (fMRI). With regard to working memory tasks, Schweitzer et al. [4] compared regional cerebral blood flow (rCBF) changes in six adult patients with ADHD and six healthy controls using [15O] H_2O positron emission tomography (PET) studies and indicated that task-related changes in rCBF in the healthy controls were more prominent in the frontal and temporal regions. Thus, it is possible that ADHD patients have functional frontal dysfunction.

However, functional brain imaging methodologies, such as PET, SPECT, and fMRI have the disadvantage of requiring large apparatuses, which prevents their use in a bedside setting for diagnostic and treatment purposes. Furthermore, these functional brain imaging methodologies do not offer high time resolution. By contrast, multi-channel near-infrared spectroscopy (NIRS) systems have recently been developed to allow non-invasive and bedside functional mapping of the cerebral cortex, with a high time resolution [5–7].

Some NIRS studies in ADHD patients have been performed using several executive function tasks. Weber et al. [8] examined prefrontal dysfunction in ADHD children as measured by NIRS and determined cerebral hemodynamic changes in response to an executive function task (trail-making test) in 11 children with ADHD and 9 healthy age- and sex-matched controls. They found that both groups showed increases in oxyhemoglobin (oxy-Hb) and CBV, but only the controls showed an additional increase in total-Hb in the left prefrontal region. Another report examined lateral prefrontal activation in 13 adult patients with ADHD and 13 healthy age- and sex-matched controls during a working memory task (n-back task) [9]. They showed that ADHD patients exhibited reduced task-related increases in the concentration of oxy-Hb in NIRS channels located over the ventrolateral prefrontal cortex, confirming previous findings of prefrontal cortical and working memory deficits in ADHD patients and arguing for a specific impairment of this clinical group in a particular working memory component. Schecklmann et al. [10] examined executive functions in 14 ADHD adults and 14 healthy age- and sex-matched controls using verbal fluency tasks. They reported that ADHD patients had a lower magnitude of oxygenation and a significant negative correlation of brain activity with performance, indicating that these results might be interpreted as an expression of a benefit in the ADHD group. Thus, functional prefrontal dysfunction in ADHD patients has been reported using NIRS.

Schroeter et al. [11] examined hemodynamic responses during incongruent, congruent, and neutral trials of the Stroop task using NIRS in 14 adult healthy controls and reported that the hemodynamic response was stronger during incongruent trials compared with congruent and neutral trials of the Stroop task in the lateral prefrontal cortex bilaterally. Thus, the stronger hemodynamic response was interpreted as stronger brain activation during incongruent trials of the Stroop task because of interference.

To our knowledge, however, there is no report examining the hemodynamic response in healthy children and functional prefrontal dysfunction in ADHD children as measured by NIRS using the Stroop task. Thus, we examined two points in the present study: (1) whether brain activation in healthy children during the Stroop color-word task is similar to healthy adults as measured by NIRS and (2) whether functional prefrontal dysfunction in ADHD children is found during the Stroop color-word task as measured by NIRS. We therefore used multichannel NIRS machines to examine the frontal characteristics of rCBV changes during the Stroop color-word task in ADHD children and age- and sex-matched control subjects.

Methods

Subjects

Twenty subjects (18 boys and 2 girls), aged 6–13 years and diagnosed with ADHD according to DSM-IV [12], were compared with 20 age- and sex-matched healthy control subjects (17 boys and 3 girls), aged 6–13 years (Table 1).

The subjects with ADHD, who had no history of developmental disorder treatment, consulted an experienced pediatric psychiatrist at the Department of Psychiatry of Nara Medical University with a chief complaint of attention deficit, hyperactivity, or impulsiveness. The subjects with ADHD underwent a standard clinical assessment comprising a psychiatric evaluation, a structured diagnostic interview, a cognitive battery, and a medical history. Two experienced pediatric psychiatrists confirmed the diagnosis of ADHD according to DSM-IV [12]. Thus, 20 subjects with ADHD who had no previous medication were enrolled in the present study. Of them, two subjects had comorbid obsessive compulsive disorder (OCD), and one subject had comorbid oppositional defiant disorder (ODD).

Healthy control subjects were recruited from local elementary schools. They also underwent a standard clinical assessment comprising a psychiatric evaluation, a structured diagnostic interview, a cognitive battery, and a medical history. Thus, 20 healthy control subjects, who were not confirmed ADHD and had no history of psychiatric or neurological disorder, were enrolled in the present study.

The Wechsler Intelligence Scale for Children-Third Edition (WISC-III) full IQ scores of subjects were all over 70. All subjects were right-handed and Japanese. This study was approved by the Institutional Review Board of Nara Medical University Hospital. Written informed consent was obtained from all subjects and/or their parents before the study.

Table 1 Characteristics of the subjects

	ADHD Mean (SD)	Control Mean (SD)	*P* value
Sex [M:F]	20 [18:2]	20 [17:3]	0.64
Age	9.55 (1.93)	9.35 (2.13)	0.76
WISC-III	99.60 (11.28)	97.65 (9.61)	0.56
ARI	15.10 (5.06)	1.65 (1.79)	<0.001§
ARH	12.05 (3.98)	0.40 (0.88)	<0.001§
ARF	27.15 (7.16)	2.05 (2.35)	<0.001§
SCWC-1	29.30 (8.39)	36.15 (7.50)	0.0097***
SCWC-2	31.70 (10.59)	39.40 (9.84)	0.022*
SCWC-3	29.75 (9.98)	36.25 (9.66)	0.043*

Group differences tested with *t* tests

ADHD Attention-deficit/hyperactivity disorder, *M* male, *F* female, *WISC-III* Wechsler Intelligence Scale for Children-Third Edition, *ARI* ADHD RS IV-J Inattention subscale's scores, *ARH* ADHD RS IV-J Hyperactivity–Impulsivity subscale's scores, *ARF* ADHD RS IV-J Full scores, *SCWC-1* Stroop color-word task number of correct answers first time, *SCWC-2* Stroop color-word task number of correct answers second time, *SCWC-3* Stroop color-word task number of correct answers third time

$*P < 0.05$; $**P < 0.02$; $***P < 0.01$; $^{\S}\ P < 0.001$

Assessment of ADHD Symptoms

ADHD Rating Scale-IV-Japanese Version (ADHD RS-IV-J, Home Version) [13] was used to evaluate ADHD behavior symptoms in ADHD children. ADHD RS-IV-J consists of 18 items regarding attention-deficit, hyperactivity, or impulsiveness, each scored on a 0–3 point scale. The total scores were calculated by adding the scores of the 18 items. The Inattention subscale's scores were calculated by adding the scores of the 9 odd-numbered items. The Hyperactivity–Impulsivity subscale's scores were calculated by adding the scores of the 9 even-numbered items. The full score, Hyperactivity–Impulsivity subscale's score, and Inattention subscale's score of ADHD RS-IV-J were 54, 27, and 27 points, respectively; it is generally considered that the higher an ADHD RS-IV-J score, the more severe the ADHD symptoms.

Twenty-six subjects (23 boys and 3 girls) diagnosed with ADHD were compared with 11 healthy control subjects (6 boys and 5 girls) to estimate the utility of ADHD RS-IV-J (Home Version). ADHD RS-IV-J exhibited a high level of reliability (Cronbach's alpha coefficient of internal consistency reliability, 0.92). The intra-class correlation was judged to be very high because the score was 0.97. The scores estimated by their mothers were significantly correlated to the scores estimated by the experienced pediatric psychiatrists (Spearman's ρ, 0.92). Furthermore, 2,709 boys (aged 6–15 years) and 2,870 girls (aged 6–15 years) were estimated by their parents using ADHD RS-IV-J (Home Version). In boys, the mean score was 6.68 (SD, 6.91; median, 5; 90th percentile, 16). In girls, the mean score was 4.38 (SD, 5.17; median, 3; 90th percentile, 11). The cutoff score of the full scoring of ADHD RS-IV-J (Home Version) was established as 14–16 points from these results.

All subjects underwent assessment for ADHD RS-IV-J (Table 1). As shown in Table 1, the scores of ADHD RS IV-J Inattention subscale's scores (ARI), ADHD RS IV-J Hyperactivity–Impulsivity subscale's scores (ARH), and ADHD RS IV-J Full scores (ARF) in the ADHD group were significantly higher than those in the control group. The ARF scores of all ADHD subjects were over 16; those of all the control subjects were under 7.

The Stroop Color-Word Task

We reproduced the Stroop task according to the method previously described [14]. The Stroop task consisted of two pages stapled together. Each page had 100 items in 5 columns of 20 items. Items on the first page were the color words RED, GREEN, and BLUE in black ink. Items on the second page were the words RED, GREEN, and BLUE printed in red, green, or blue ink, with the limitation that the word and ink could not match. On the two pages, the items were randomly distributed, except that no item within a column could follow itself.

Before the task, examiners instructed subjects as follows: "These are tests of how quickly you can read the words on the first page, and the colors on the second page. After we say 'begin,' you are to read down the columns, starting with the first one, saying the words/colors to yourself as quickly as you can. After you finish the first column, go on to the next and so on. After you have read the paper for 45 s, we will turn the page. Then you will read the turned paper again. And we will repeat this process with you."

We combined those two pages and made the Stroop color-word task simple and easy because the subjects were school-age children, including 6 year olds. The Stroop color-word task consisted of the first page (p1) and the second page (p2). The Stroop color-word task consisted of a 45-s p1 task, a 45-s p2 task (the color-word task first time), a 45-s p1 task, a 45-s p2 task (the color-word task second time), a 45-s p1 task, a 45-s p2 task (the color-word task third time), and a 45-s p1 task. We made the 45-s p1 task as the baseline task. We also counted the number of correct answers each time. We named them as follows: Stroop color-word task number of correct answers first time (SCWC-1), second time (SCWC-2), and third time (SCWC-3). Examiners who were blind to diagnoses measured the Stroop color-word task. As shown in Table 1, the SCWC-1, SCWC-2, and SCWC-3 of the ADHD group were significantly lower than those of the control group.

NIRS Measurements

The oxy-Hb increase and deoxyhemoglobin (deoxy-Hb) decrease in NIRS have been shown to reflect cortical activation. In animal studies, oxy-Hb is the most sensitive indicator of rCBF because the direction of change in deoxy-Hb is determined by the degree of changes in venous blood oxygenation and volume [15]. Therefore, we decided to focus on changes in oxy-Hb. In this study, oxy-Hb was measured with a 24-channel NIRS machine (Hitachi ETG-100, Hitachi Medical Corporation, Tokyo, Japan) at two wavelengths of near-infrared light (760 and 840 nm), the absorption of which was measured. Oxy-Hb was calculated as previously described [4]. The interprobe distance of the machine was 3.0 cm, and it was determined that the machine measures points 2–3 cm beneath the scalp, i.e., the surface of the cerebral cortices [16, 17].

The NIRS probes were placed on the subject's frontal regions, and arranged to measure the relative concentrations of Hb changes at 24 measurement points in an 8 × 8 cm area, with the lowest probes positioned along the Fp1–Fp2 line according to the international 10/20 system used in electroencephalography. The correspondence of the probe positions and the measurement points on the cerebral cortex were confirmed by superimposition of the probe positions on an MRI of a three-dimensionally reconstructed cerebral cortex of a representative subject in the control group (Fig. 1). The absorption of near-infrared light was measured with a time resolution of 0.1 s. The obtained data were analyzed with the "integral mode": the pre-task baseline was determined as the mean across 10 s just before

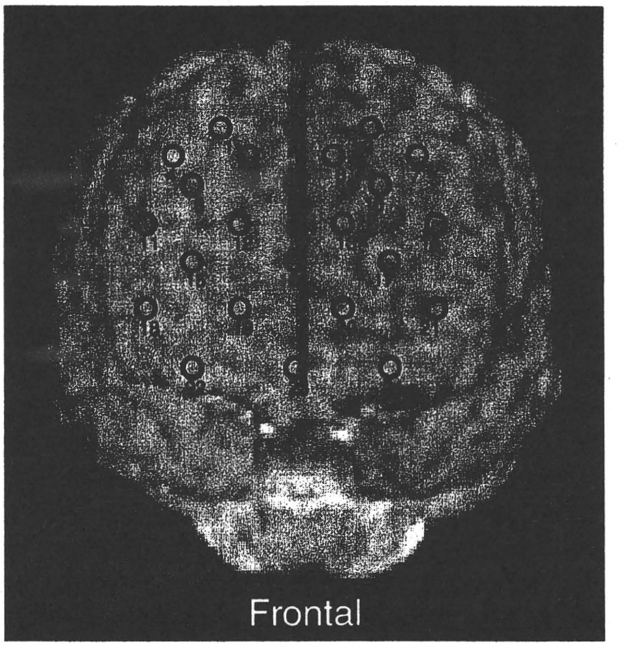

Fig. 1 Cortical projection of near-infrared spectroscopy (NIRS) measurement points. The points were mapped onto anatomical frontal brain using MRIcro software (MRIcro: developed by Dr Chris Rorden, available at http://www.mricro.com). *Numbers* denote channel numbers for points of measurement

the task period; the post-task baseline was determined as the mean across 25 s after the task period; and linear fitting was performed on the data between the two baselines. Moving average methods were used to exclude short-term motion artifacts in the analyzed data (moving average window, 5 s).

We tried to exclude motion artifacts by closely monitoring artifact-evoking body movements, such as neck movements, strong biting, and blinking (identified as most influential in the preliminary artifact-evoking study), and by instructing the subjects to avoid these movements during the NIRS measurements. Examiners who were blind to diagnoses measured NIRS.

Statistical Analyses

Oxy-Hb changes were compared between each of the two groups with Student's *t*-tests using the grand average waveforms every 0.1 s in each channel. This analysis enabled more detailed comparison of oxy-Hb changes along the time course of the task. Data analyses were conducted using MATLAB 6.5.2 (Mathworks, Natick, MA, USA) and Topo Signal Processing type-G version 2.05 (Hitachi Medical Corporation, Tokyo, Japan). OT-A4 version 1.63 K (Hitachi Medical Corporation, Tokyo, Japan) was used for overlap display of the grand average waveforms in both groups in Fig. 2 and was used to calculate mean oxy-Hb measurements in Table 3. SPSS 16.0 J for Windows (SPSS, Tokyo, Japan) was used for statistical analysis.

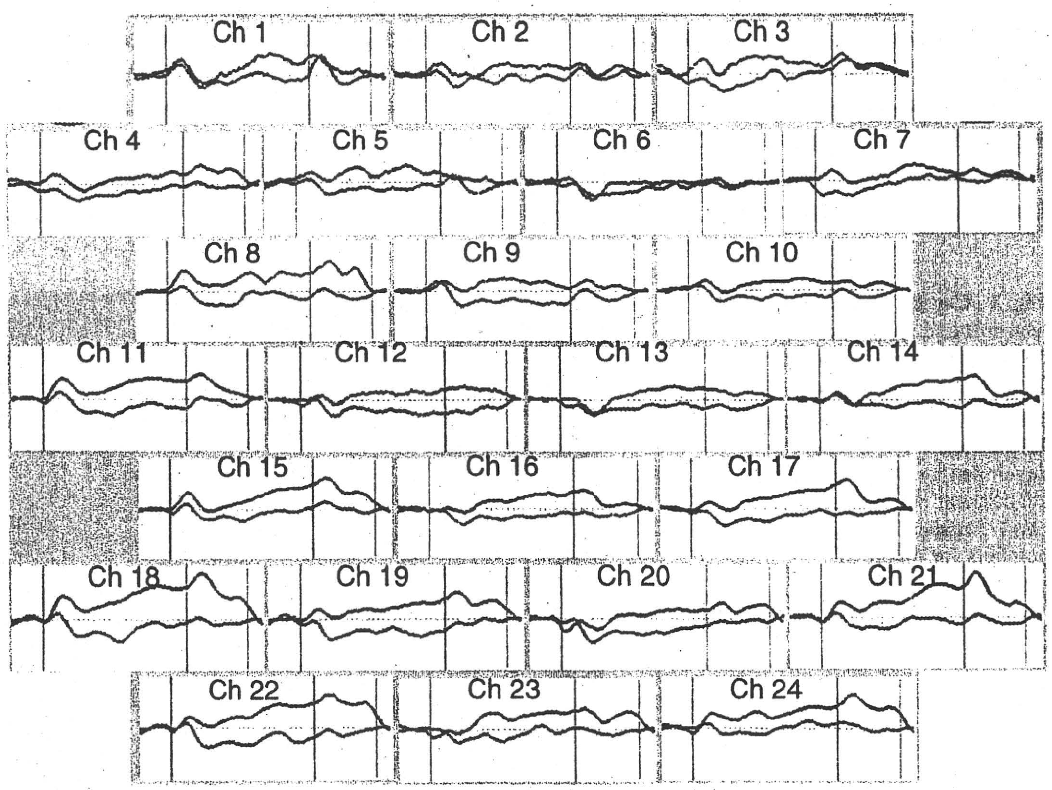

Fig. 2 Grand average waveforms of oxyhemoglobin (oxy-Hb) concentration changes during the Stroop color-word task in both groups. Grand average waveform of oxy-Hb in the attention-deficit/hyperactivity disorder (ADHD) group is the *red line*, and grand average waveform of oxy-Hb in the control group is the *blue line*. The task conducts between *light green lines*

Table 2 Correlations between Stroop task and characteristics of the subjects

	ADHD			Control		
	SCWC-1	SCWC-2	SCWC-3	SCWC-1	SCWC-2	SCWC-3
Age	0.547**	0.519**	0.433	0.777§	0.763§	0.726§
WISC-III	0.088	0.037	−0.069	−0.058	0.196	0.273
ARI	0.22	0.222	−0.091	−0.288	−0.216	−0.193
ARH	−0.052	−0.108	−0.205	−0.152	−0.156	−0.297
ARF	0.068	0.064	−0.217	−0.295	−0.221	−0.215

Correlations between Stroop task and characteristics of the subjects tested with Spearman's correlation test

ADHD Attention-deficit/hyperactivity disorder, *M* male, *F* female, *WISC-III* Wechsler Intelligence Scale for Children-Third Edition, *ARI* ADHD RS IV-J Inattention subscale's scores, *ARH* ADHD RS IV-J Hyperactivity–Impulsivity subscale's scores, *ARF* ADHD RS IV-J Full scores, *SCWC-1* Stroop color-word task number of correct answers first time, *SCWC-2* Stroop color-word task number of correct answers second time, *SCWC-3* Stroop color-word task number of correct answers third time

* $P < 0.05$; ** $P < 0.02$; *** $P < 0.01$; § $P < 0.001$

Results

Correlations Between Stroop Task and Characteristics of the Subjects

Spearman's ρ correlations between the scores of SCWC and age, WISC-III, and the scores of ADHD RS IV-J can be seen in Table 2. In both groups, there are positive correlations between the scores of SCWC and age; there are no correlations between the scores of SCWC and WISC-III and between the scores of SCWC and the scores of ADHD RS IV-J.

NIRS Data of the Subjects During the Stroop Color-Word Task

The grand average waveforms of oxy-Hb concentration changes during the Stroop color-word task in both groups can be seen in Fig. 2. The grand average waveform of oxy-Hb concentration change in the control group increased during the task period. On the other hand, that of the ADHD group did not change much. The mean oxy-Hb measurements from task to post-task period in all 24 channels can be seen in Table 3. Group differences were tested with Bonferroni correction. From task to post-task period, the mean oxy-Hb of the ADHD group was significantly smaller than that in the control group in channels 18, 21, and 22. Topographic presentation of the t value of oxy-Hb comparison between the control group and the ADHD group during the Stroop color task can be seen in Fig. 3. The oxy-Hb changes in the control group were significantly greater than that of the ADHD group during the task period in the inferior prefrontal cortex, especially in the inferior lateral prefrontal cortex bilaterally.

Discussion

Until now, there have been few reports examining prefrontal dysfunction in ADHD children as measured by NIRS. In one, cerebral hemodynamic changes were examined in response to an executive function task (trail-making test) in 11 children with ADHD and 9 healthy age- and sex-matched controls [8]. In that study, both groups showed increases in

Table 3 Mean oxyhemoglobin (oxy-Hb) measurements from task to post-task period in 24 channels

	Control		ADHD		Statistical analysis
	Mean (mMmm)	SD (mMmm)	Mean (mMmm)	SD (mMmm)	
Ch1	0.0231	0.02957	−0.0031	0.04273	NS
Ch2	0.0172	0.05376	−0.0061	0.02842	NS
Ch3	0.0274	0.04375	−0.0037	0.05009	NS
Ch4	0.0185	0.03762	−0.0175	0.04418	NS
Ch5	0.0212	0.03208	−0.0134	0.03826	NS
Ch6	−0.0090	0.03770	−0.0141	0.03425	NS
Ch7	0.0152	0.04812	−0.0079	0.05385	NS
Ch8	0.0444	0.10645	−0.0138	0.03051	*
Ch9	0.0137	0.03206	−0.0211	0.02840	NS
Ch10	0.0147	0.03342	−0.0159	0.03312	NS
Ch11	0.0355	0.02300	−0.0167	0.03325	NS
Ch12	0.0128	0.02828	−0.0278	0.04339	NS
Ch13	0.0051	0.02990	−0.0190	0.03809	NS
Ch14	0.0249	0.02102	−0.0116	0.03667	NS
Ch15	0.0379	0.02859	−0.0078	0.03673	NS
Ch16	0.0176	0.03181	−0.0208	0.03619	NS
Ch17	0.0300	0.03126	−0.0196	0.03569	NS
Ch18	0.0647	0.06864	−0.0189	0.06022	§
Ch19	0.0311	0.05739	−0.0261	0.03934	*
Ch20	0.0094	0.03978	−0.0256	0.04434	NS
Ch21	0.0529	0.04550	−0.0122	0.03573	§
Ch22	0.0465	0.05556	−0.0256	0.05184	§
Ch23	0.0299	0.04915	−0.0123	0.05563	NS
Ch24	0.0478	0.04947	−0.0012	0.04019	NS

Group differences were tested with Bonferroni correction

* $P < 0.1$; ** $P < 0.05$; *** $P < 0.01$; § $P < 0.001$

oxy-Hb and CBV, but only the controls showed an additional increase in total-Hb in the left prefrontal region. In the present study, we used the Stroop color-word task to estimate prefrontal function because the inferior frontal gyrus has been described as one of the regions most strongly related to Stroop interference [18]. To the best of our knowledge, there are no other studies using the Stroop task to examine prefrontal dysfunction in children with ADHD as measured by NIRS.

With respect to the relationship between ADHD and the Stroop task, Schwartz and Verhaeghen [19] examined 25 studies that reported data on the Stroop color word task in children and adults with ADHD and in age-matched controls. ADHD individuals were found to be 1.14 times slower on average than age-matched controls in both the color and the color-word condition, while the Stroop interference effect appeared to be immune to age in both groups. Similar results were obtained in the present study. SCWC-1, SCWC-2, and SCWC-3 of the ADHD group were significantly lower than those of the control group. Furthermore, we examined Spearman's ρ correlations between the scores of SCWC and age, WISC-III, and the scores of ADHD RS IV-J, which indicated that there are positive

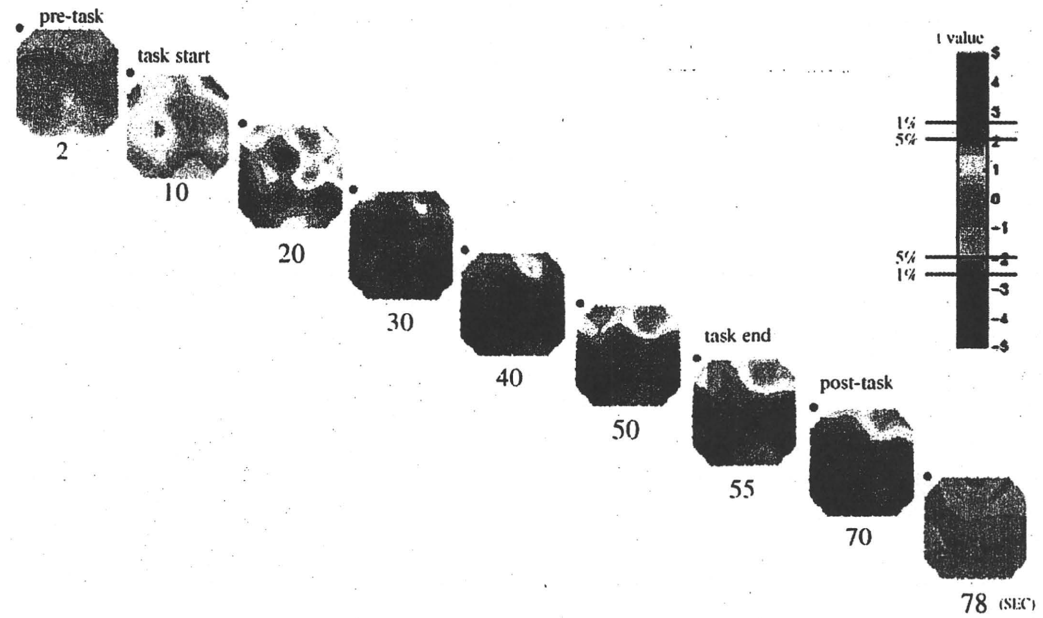

Fig. 3 Topographic presentation of the *t* value of oxyhemoglobin (oxy-Hb) comparison between the control group and the attention-deficit/hyperactivity disorder (ADHD) group during the Stroop color-word task. The *t* value of oxy-Hb for the control and ADHD group is presented as a topographic map along the time course of the task (from top to bottom). The *red*, *green*, and *blue* areas in the topographs indicate positive, zero, and negative *t* values, with 2.0 and 2.7 for 5% and 1% statistical significance levels, respectively

correlations between the scores of SCWC and age in both the groups. These data suggest that our Stroop color-word task may be a useful task for estimating ADHD symptoms.

Despite the relationship between the Stroop color-word task and NIRS, there are few studies that have examined the relationship. Ehlis et al. [20] investigated 10 healthy subjects by means of multi-channel NIRS during performance of congruent and incongruent trials of the Stroop color-word task. In that study, oxy-Hb and total-Hb changes indicated specific activation for interference trials in inferior-frontal areas of the left hemisphere. However, the influences of the Stroop color-word task in inferior-frontal areas of the right hemisphere were not examined. As previously mentioned, the other study [11] reported the hemodynamic response in the lateral prefrontal cortex bilaterally.

However, these two studies reported that oxy-Hb change in adult healthy subjects indicated specific activation during the Stroop color-word task in inferior-frontal areas. In the present study, we found that oxy-Hb change in 20 healthy children indicated specific activation during the Stroop color-word task in the inferior prefrontal cortex, especially in the inferior lateral prefrontal cortex bilaterally, supporting the Schroeter et al study. We therefore found prefrontal brain activation in healthy children during the Stroop color-word task as well as in healthy adults using NIRS, which was interpreted as a result of Stroop interference in children as well as in adults.

We also discussed the comparison between the ADHD group and the control group. We found that oxy-Hb changes in 20 ADHD children were smaller than those in 20 healthy children during the Stroop color-word task in the inferior prefrontal cortex, especially in the inferior lateral prefrontal cortex bilaterally. As shown in Table 1, SCWC-1, SCWC-2, and SCWC-3 of the ADHD group were significantly lower than those of the control group. These data suggest that the prefrontal brain activation in the ADHD children may not fulfill function well during the Stroop color-word task. indicating that ADHD children have some problems in the inferior prefrontal cortex, especially in the inferior lateral prefrontal cortex bilaterally, which has been described as one of the regions most strongly related to Stroop interference.

In the present study, we had two restrictions: NIRS has disadvantages compared with other methodologies [7]. The main disadvantage of NIRS is that it enables measurement of Hb concentration changes only as relative values, not as absolute values. We made the Stroop task that had the first page as the base task to overcome these potential problems. Furthermore, we measured Hb concentration changes from the activation task to the base task and performed the task three times to average potential accidental changes and prevent the subjects from being tired. The other restriction was the inclusion of subjects with comorbidity (i.e., two subjects had comorbid OCD; one subjects had comorbid ODD). Future studies are needed to compare between pure ADHD children and ADHD children with comorbid disorders (e.g. OCD, ODD, and PDD).

Finally, our findings of prefrontal dysfunction in ADHD by NIRS involved a large group, allowing for high confidence in the data. The Stroop color-word task may be a very useful tool when measuring prefrontal dysfunction in ADHD using NIRS, and multi-channel NIRS systems may be one very useful measurement to assess brain function, especially for children, because multi-channel NIRS systems can provide handy, non-invasive, and bed-side-functional mapping of the cerebral cortex at much shorter measurement time (about 5 min) than other functional brain imaging methodologies. Future studies are needed to determine the effect of osmotic-release methylphenidate (MPH) treatment on ADHD children using NIRS by comparing before and after osmotic-release MPH treatment.

Summary

The purpose of the present study was to examine the hemodynamic response in healthy children and functional prefrontal dysfunction in ADHD children as measured by NIRS using the Stroop task. Therefore, 20 medication-naïve children with ADHD and 20 age- and sex-matched healthy control subjects participated in the present study. The relative concentrations of oxy-Hb were measured with frontal probes every 0.1 s during the Stroop color-word task, using 24-channel NIRS machines. Findings indicate that ADHD children have some problems in the inferior prefrontal cortex, especially in the inferior lateral prefrontal cortex bilaterally, which has been described as one of the regions most strongly related to Stroop interference. Finally, the Stroop color-word task during NIRS may be one useful measurement to assess prefrontal brain dysfunction in ADHD children. Furthermore, multi-channel NIRS systems may be one very useful measurement to assess brain function, especially for children, because multi-channel NIRS systems can provide handy, non-invasive, and bedside-functional mapping of the cerebral cortex at much shorter measurement time (about 5 min) than other functional brain imaging methodologies.

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Regular Article

Effects of osmotic-release methylphenidate in attention-deficit/hyperactivity disorder as measured by event-related potentials

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Aim: Attention-deficit/hyperactivity disorder (ADHD) is a relatively common central nervous system disorder in school-age children, which may involve a specific disorder in cognition and/or information processing. Event-related potentials (ERP) are commonly used as physiological measures of cognitive function as they are easily measured and non-invasive. Thus, in the present study, we examined the effects of osmotic-release methylphenidate (MPH) (Concerta), a common treatment for childhood attention-deficit/hyperactivity disorder (ADHD), in ADHD children as measured by ERP.

Methods: Ten ADHD children participated after giving consent. Based on the guidelines for evoked potential measurement, mismatch negativity (MMN) and P300 were obtained by auditory odd-ball tasks. We measured both MMN and P300 in the drug-naive condition and after intake of osmotic-release MPH.

Results: The MMN amplitudes after intake of osmotic-release MPH were significantly greater than those in the drug-naive situation at Pz and C4. The P300 amplitudes after intake of osmotic-release MPH were significantly greater than those in the drug-naive situation at Cz and Pz.

Conclusion: MMN and P300 are sensitive tools for measuring the pharmacological effects of osmotic-release MPH in ADHD children.

Key words: attention-deficit/hyperactivity disorder, event-related potentials, methylphenidate, mismatch negativity, P300.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) is a central nervous system (CNS) disorder estimated to occur in 3–7% of school-age children,[1] and is considered to involve a specific disorder in cognition and/or information processing. Event-related potentials (ERP) are commonly used as physiological measures of cognitive function as they are easily measured and non-invasive. For instance, ERP have been used to examine cognitive disturbance in children with developmental disorder, and an early negative ERP has been shown to be strongly-related to attention deficit.

The mismatch negativity (MMN), which functions in a distinctive stimulus discrimination process that utilizes sensory memory of prior stimuli, is considered an important mechanism for rapid detection of changes in the outer world, except those concerning consciousness.[2] As such, MMN reflects an automatic cerebral discrimination process, not under-attentive control. We previously reported that the amplitudes of both P300 and MMN were smaller in ADHD patients than in healthy subjects.[3]

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With respect to the impulsivity observed in ADHD patients, we previously reported that the Hyperactivity-Impulsivity subscale score of the ADHD Rating Scale-IV-Japanese version (ADHD RS-IV-J) (Home Version)[4] had a significantly strong positive correlation with the latency of MMN, and had a significant strong negative correlation with the amplitude of MMN, in predominantly hyperactive-impulsive type ADHD subjects.[5] In other words, the more severe the impulsivity of ADHD subjects, the longer the MMN latency and the lower the MNN amplitude. Thus, ADHD children may have difficulty in referring to previous stimuli, causing increased sensitivity to and augmented anxiety about stimuli, which may account for the exhibited impulsivity.

Stimulating medications are commonly used for treatment of ADHD symptoms. Methylphenidate (MPH), for instance, has been used in ADHD children since 1937.[6] In Japan, osmotic-release MPH (Concerta) was recently accepted as a treatment medication for ADHD children. Several studies have demonstrated a reduced P300 in ADHD children, which was normalized following MPH medication.[7–9] However, to the best of our knowledge the effects of osmotic-release MPH on MMN in ADHD children have not been described. Thus, in the present study we examined the effects of MPH on MMN and P300, and on ameliorating cognitive function, especially attention function, in ADHD children.

METHODS

Subjects

Ten children (nine boys, one girl) aged 7–13 years and diagnosed as ADHD based on DSM-IV,[10] participated in the present study. The subjects with ADHD, who had no history of developmental disorder treatment, consulted an experienced pediatric psychiatrist (M. S., T. O., or H. N.) at the Department of Psychiatry of Nara Medical University with the chief complaint of attention deficit, hyperactivity, or impulsiveness. The subjects with ADHD underwent a standard clinical assessment comprising a psychiatric evaluation, a structured diagnostic interview, a cognitive battery, and a medical history. Two experienced pediatric psychiatrists (J. I., H. N.) confirmed the diagnosis of ADHD according to DSM-IV.[10]

The Wechsler Intelligence Scale for Children-Third Edition (WISC-III) full IQ scores of all subjects were over 70. All patients were Japanese and right-handed. In ADHD subjects, the severity of ADHD symptoms and latencies and amplitudes of ERP (MMN, P300) were estimated both before and after (8–12 weeks) osmotic-release MPH treatment at the same time of day (10.00–11.00 hours). ADHD subjects were treated with osmotic-release MPH as soon as possible after baseline ERP. The dose of osmotic-release MPH treatment ranged from 18 to 54 mg (mean ± SD, 33.3 ± 10.4 mg). The characteristics of the subjects can be seen in Table 1. This study was approved by the Institutional Review Board of Nara Medical University Hospital. Written informed consent was obtained from all subjects and/or their parents prior to the study.

Procedures

ADHD assessment

We used the ADHD RS-IV-J (Home Version)[4] to evaluate ADHD symptoms in ADHD children. It is generally considered that the higher an ADHD RS-IV-J score, the more severe the ADHD symptoms. All subjects underwent ADHD RS-IV-J assessment before and after osmotic-release MPH treatment (Table 1). In ADHD children the ADHD RS-IV-J full scores (ARF), ADHD RS-IV-J inattention subscales scores (ARI), and the ADHD RS-IV-J hyperactivity-impulsivity subscales scores (ARH) were significantly higher before osmotic-release MPH treatment than those after osmotic-release MPH treatment.

Event-related potentials

Measurements

Based on the guidelines for evoked potential measurement, MMN and P300 were obtained by auditory odd-ball tasks. An NEC Multi Stim II (NEC, Tokyo, Japan) was used as the auditory stimulus system.

MMN

Tone bursts at 1000 Hz standard stimuli ($P = 0.9$) and at 1100 Hz deviant stimuli ($P = 0.1$) (each stimulus lasted 50 ms) were presented at 500-ms intervals and at 80-dB intensities. The infrequent and frequent stimuli were given in random order via headphones. The MMN was measured while the children, as instructed, were reading books or magazines of their choice, without paying particular attention to the auditory stimuli given.

Table 1. Subjects characteristics

Sex	Boy	%	Girl	%	
($n = 10$)	9	90	1	10	
	Mean		SD		
Age (years)	9.3		1.9		
WISC-III	100.5		15.3		
Concerta dose (mg)	33.3		10.4		

	Before Concerta treatment		After Concerta treatment			
	Mean	SD	Mean	SD	t value (d.f. = 9)	*P*-value
ARF	31.1	8	11.9	5.6	9.826	<0.001
ARI	17.5	5.5	8.3	3.1	6.209	<0.001
ARH	13.6	3.6	3.6	3.8	8.135	<0.001

ARF, Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Japanese version full scores; ARH, Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Japanese version hyperactivity-impulsivity subscale scores; ARI, Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Japanese version inattention subscale scores; WISC-III, Wechsler Intelligence Scale for Children-Third Edition.

P300

Infrequent target stimuli were presented as tone bursts at 2000 Hz ($P = 0.2$) and frequent non-target stimuli as bursts at 1000 Hz ($P = 0.8$), with each stimulus lasting 50 ms. Both types of stimuli were given at intervals of 1.5 s and an intensity of 80 dB. The infrequent and frequent stimuli were given in random order via headphones. The children were instructed to pay attention to the target stimuli with their eyes open, and to press the button as quickly as possible when each target stimulus was delivered.

Recording and analyses

ERP were recorded with an MEB 2200 (NIHON KOHDEN, Tokyo, Japan). Electroencephalograms (EEG) were obtained at Fz, Cz, C3, C4, and Pz positions on the scalp using disk electrodes. The bilateral ear lobes were used as the reference electrode sites. The resistance of the electrodes was set at ≤5 kΩ. MMN was analyzed during the period between the 30-ms pre-stimulus and the 360-ms post-stimulus. P300 was analyzed during the period between 50 ms pre-stimulus and 750 ms post-stimulus. Artifact-free responses to the stimuli were added and averaged after EEG amplitude data ≥100 μV and eye movements were removed. To prevent the subjects from getting tired of, or used to, performing the tasks, each trial was conducted only once.

MMN

Fifty responses to infrequent deviant stimuli and 450 responses to frequent standard stimuli were averaged separately. The waveform of the frequent standard stimuli responses was subtracted from that of the infrequent deviant stimuli responses. From the subtraction waveform, MMN was identified as a negative wave with a peak latency from 100 to 250 ms. MMN latency and amplitude were measured.

P300

Thirty responses to infrequent target stimuli were averaged. Of the ERP obtained, P300 was identified as a positive wave with a peak latency from 250 to 550 ms. P300 latency and amplitude were also measured.

Statistical analyses

Statistical comparison of subject characteristics between the two groups was performed by two-tailed paired *t*-test. The latencies and amplitudes of both P300 and MMN were compared between before treatment and after treatment by two-tailed paired *t*-test. SPSS 17.0 J for Windows (SPSS, Tokyo, Japan) was used for all analyses.

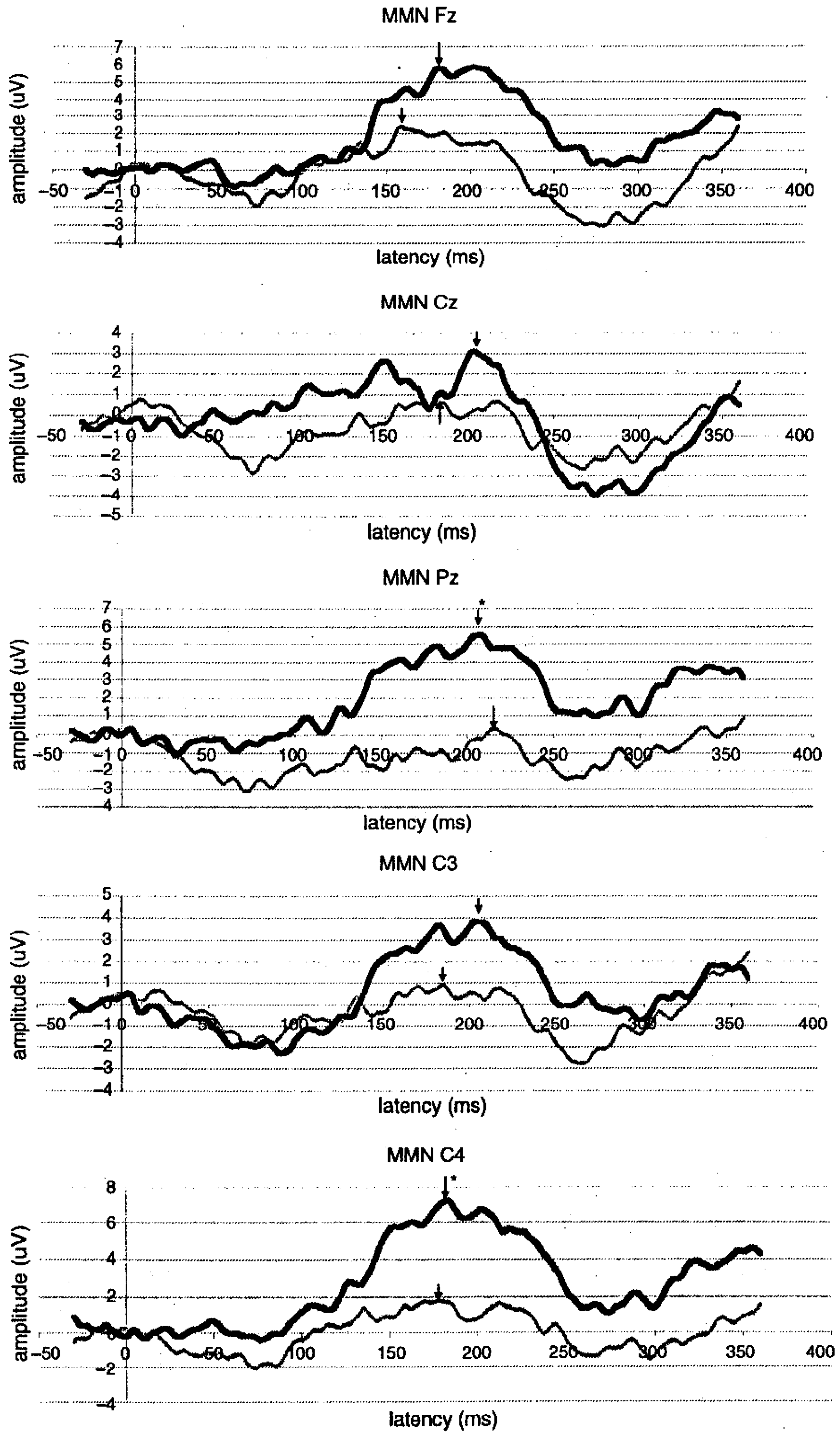

Figure 1. Grand average mismatch negativity (MMN) from attention-deficit/hyperactivity disorder children (▬) before and (▬) after Concerta treatment conditions. MMN is shown by arrows. *$P < 0.05$.