11) Lopez BR, Lincoln AJ, Ozonoff S, Lai Z. Examining the relationship between executive functions and restricted, repetitive symptoms of autistic disorder. J Autism Dev Disord 2005 ; 35 : 445-60.
12) Pennington BF, Ozonoff S. Executive functions and developmental psychopathologies. J Child Psychol Psychiatry 1996 ; 37 : 51-87.
13) Shafritz KM, Dichter GS, Baranek GT, Belger A. The neural circuitry mediating shifts in behavioral response and cognitive set in autism. Biol Psychiatry 2008 ; 63 : 974-80.
14) Marco EJ, Hinkley LB, Hill SS, Nagarajan SS. Sensory processing in autism : a review of neurophysiologic findings. Pediatr Res 2011 ; 69 : 48-54.
15) Takahashi H, Nakahachi T, Kamio Y, et al. Hyperreactivity to weak acoustic stimuli and prolonged acoustic startle latency in children with autism spectrum disorders. Mol Autism 2014 ; 5 : 23.
16) 高橋秀俊，神尾陽子．自閉症のエンドフェノタイプ．精神保健研究 2014；27：27-33.
17) 神尾陽子．発達障害の神経心理—自閉症スペクトラム障害の発達認知神経科学的理解．神経心理学 2008；24：32-9.
18) de Lacy N, King BH. Revisiting the relationship between autism and schizophrenia : toward an integrated neurobiology. Annu Rev Clin Psychol 2013 ; 9 : 555-87.
19) Hollander E, Wang AT, Braun A, et al. Neurological considerations : autism and Parkinson's disease. Psychiatry Res 2009 ; 170 : 43-51.
20) Cerejeira J, Lagarto L, Mukaetova-Ladinska EB. Behavioral and psychological symptoms of dementia. Front Neurol 2012 ; 3 : 73.
21) James IA, Mukaetova-Ladinska E, Reichelt FK, et al. Diagnosing Aspergers syndrome in the elderly : a series of case presentations. Int J Geriatr Psychiatry 2006 ; 21 : 951-60.
22) 萩原徹也，荻原朋美，田中　章，ほか．自閉症スペクトラム障害の特性が認められた82歳の女性症例．精神科治療学 2012；27：647-53.
23) Mukaetova-Ladinska EB, Perry E, Baron M, et al. Ageing in people with autistic spectrum disorder. Int J Geriatr Psychiatry 2012 ; 27 : 109-18.
24) 岡田　俊．精神病症状を伴う思春期・成人期の自閉症スペクトラム障害の診断と介入．臨床精神薬理 2013；16：345-55.
25) Dhossche DM, Shah A, Wing L. Blueprints for the assessment, treatment, and future study of catatonia in autism spectrum disorders. Int Rev Neurobiol 2006 ; 72 : 267-84.
26) Wachtel LE, Hermida A, Dhossche DM. Maintenance electroconvulsive therapy in autistic catatonia : a case series review. Prog Neuropsychopharmacol Biol Psychiatry 2010 ; 34 : 581-7.
27) Maski KP, Jeste SS, Spence SJ. Common neurological co-morbidities in autism spectrum disorders. Curr Opin Pediatr 2011 ; 23 : 609-15.
28) Gillberg C. Deficits in attention, motor control, and perception : a brief review. Arch Dis Child 2003 ; 88 : 904-10.
29) Nobile M, Perego P, Piccinini L, et al. Further evidence of complex motor dysfunction in drug naive children with autism using automatic motion analysis of gait. Autism 2011 ; 15 : 263-83.
30) Amiet C, Gourfinkel-An I, Bouzamondo A, et al. Epilepsy in autism is associated with intellectual disability and gender : evidence from a meta-analysis. Biol Psychiatry 2008 ; 64 : 577-82.

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特集　今日の自閉スペクトラム症，子どもから大人まで

Autism spectrum disorder today, from chilhood to adulthood

自閉スペクトラム症と精神科的併存症

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Key Words☞自閉スペクトラム症（autism spectrum disorder：ASD），精神科的併存症（psychiatric comorbidity）

抄録：自閉症スペクトラム障害（Autism Spectrum Disorder，以下ASD）では，多彩な精神科的併存症が認められ，主要徴候とも密接に関与しながら多彩な臨床像を形成する。したがって，ASDを有する児・成人の支援を考えるうえで，あらゆる発達段階において併存症を含めた包括的視点からの状態像把握が重要となる。本稿では，ASDにみられるさまざまな精神科的併存症について概説し，その評価・治療上の問題点についても考察を加える。

はじめに

自閉スペクトラム症/自閉症スペクトラム障害（Autism Spectrum Disorder，以下ASD）は，DSM-5では，A）複数の状況下における社会的コミュニケーションおよび対人的相互反応の持続的な欠陥，B）行動・興味・活動の限局された反復的・常同的な様式の2つの主要徴候が幼少期早期に出現する発達障害と定義され[2]，従来の自閉症，アスペルガー障害，特定不能の広汎性発達障害などの下位診断群を包含する概念である。ASDを有する児童および成人では，約70％の症例で1つ以上の精神科的または身体的併存症（comorbidity）が認められる[13]。これらの併存症の特性や重症度は，成長発達や本人を取り巻く状況（発達障害特性を考慮した支援体制の有無など）によって変化し，各ASD個人のQOLを大きく左右する因子となる。また，これらの併存症は，個人差はあるものの主要徴候と複合的に関与しながら多彩な臨床像を形成するため，各年代において主要徴候のみならず併存症も的確に把握し，包括的視点から状態像の把握を行うことが，ASDを有する児・成人の支援を考えるうえで重要である。

本稿では，ASDにみられるさまざまな精神科的併存症について概説し，その評価・治療上の問題点についても考察を加える。

ASDにみられる精神科的併存症

ASDにみられる精神科的併存症は，注意欠如多動性障害・強迫性障害・睡眠障害・チック・気分障害（うつ病，双極性障害）・パニック・癇

Psychiatric comorbidity associated with ASD

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癪・自傷行為・被害関係妄想・フラッシュバック体験(タイムスリップ現象)・カタトニア・不安障害(限局性恐怖症，全般性不安障害，社会不安障害)など非常に多岐にわたる[13]。これらの精神科的併存症には，ASDでの高い合併率が報告されている精神疾患のほか，主要徴候を背景に，発達障害特性を意識した支援が行き届かないことで二次的に出現するものまでさまざまである。以下，代表的な併存症について解説する。

1. 注意欠如多動性障害

注意欠如多動性障害(Attention-Deficit/Hyperactivity Disorder：以下AD/HD)は，従来のDSM-Ⅳ-TR[3]によると，7歳以前に始まる「不注意」と「多動・衝動性」を特徴とする発達障害と定義されていた。DSM-Ⅳ-TRでは，ASDとAD/HDは，基本的に異なる疾患概念とされ，診断の併記も認められていなかったが，実臨床場面においては，ASDにAD/HD症状を伴う頻度は決して低いとはいえず，Leyferら[14]のASDにおける精神科的併存症を調査した研究によると，クリニック通院中の109名のASD児(5～17歳：平均9.2±2.7歳)において，その72％がなんらかの併存症を有し，併存症の内訳としてAD/HDが30.6％であった。また，遂行機能の観点から両障害を比較した研究[24]により，ASD, AD/HDに共通して認められた注意の維持やWorking Memoryの障害の存在から，共通した病態が指摘されている。このような実状をふまえ，DSM-5では「ASDとAD/HDの診断併記」が認められるようになり，ASDとAD/HDの併存が疑われる症例の的確なアセスメントが，今後いっそう重要になる。野村[20]は，両障害が類似した症状を呈しうることや相互的に関与し合う可能性を意識したうえで，幼少期から現在に至るまでの生活歴や行動特性の詳細な評価を行い，AD/HD症状出現のetiologyを可能な限り明確にすることがテーラーメイドな治療方針の決定に不可欠であるとしている。たとえば，AD/HDが疑われて来院した症例において，そのASD特性がこれまで周囲から十分に理解されずに，本人への接し方や生活設定が不適切であることが，AD/HD症状出現の主要因となっている場合，まずは対応の構造化を図るなどのASD特性に応じた対応法を試みる必要がある。また，詳細は他稿に譲るが，両障害の併存が疑われる症例に対するAD/HD治療薬を用いた薬物治療も重要な治療選択肢の1つであり，併存例に対する薬物治療ストラテジーの確立が今後の重要課題である。

2. 精神病症状

ASDでは，被害関係妄想や幻覚体験などの精神病症状の併存が時にみられることが知られている。Hofvanderら[10]は，知的障害を有さないASD成人122名(16～60歳；中央値29歳)における精神科的併存症の調査研究を行い，12％に精神病性障害を認めたと報告している。ASDにおける精神病症状併存の要因として，いじめや環境への不適応を契機として状況依存的に被害的な認知に傾いてしまうことや，ASD特有の固執性の言動や反響言語が統合失調症に特徴的な徴候(対話性幻聴，独語)と誤って判断されることなどが考えられている。一方で，近年，ASDと統合失調症の間には共通した遺伝的背景の存在も示唆されており[6]，両者は相互排他的ではなく，実際に合併例もみられる。上記のように，ASDにみられる精神病症状のetiologyは多様であるため，その介入法に関するエビデンスは乏しい。ASDにおいて精神病症状を認めた場合，発達歴・臨床経過・精神病症状の色彩を総合的に判断し，ASD特性を考慮しながら十分な横断的・縦断的評価を行いながら，環境調整や薬物治療の効果を注意深く観察していくことが重要である[21]。

3. 不安障害

児童・青年期のASDでは，その11～84％において不安症状が合併すると報告されており，全般性不安障害・社交不安障害・限局性恐怖症などさまざまなタイプの不安障害の合併が報告されている[26]。前述したHofvanderら[10]

は，ASD成人患者122名の中で，不安障害の有病率は50％と，気分障害(53％)に次いで高いと報告した。その内訳は全般性不安障害18例(15％)，社交恐怖16例(13％)，パニック障害13例(11％)，限局性恐怖症7例(6％)，その他の不安障害が3例であった。不安障害の併存は，臨床サンプルにおいて高率に認められるだけでなく，地域ベースの疫学調査においても高率であるとの報告がなされている。Simonoffら[22]は，地域の一般集団56,946人から抽出した112名のASD児(10～14歳；平均12歳)に対し，併存症の有無を包括的に評価し，約70％のケースで1つ以上の精神科的併存症を有し，内訳として，社交不安障害(29.2％)が最多であったとしている。以上のように，ASDを有する児・成人双方において不安障害は高率に合併し，その出現形態は，年齢・認知機能・ASDの主要徴候の程度による影響を受ける可能性が示唆されている[26]。ASDにおける不安症状は，日常生活スキルの低下や他者との関係性構築に支障をきたし，抑うつやひきこもりの要因となりうるため[7]，ASDを有する児・成人の状態像を把握するにあたり，不安症状の評価を意識的に行う必要がある。一方，ASDの不安症状は他覚的に把握しにくく，質問紙でもスクリーニングしにくいとする報告もあり[9]，早期発見に関する課題が残る。治療については，近年Vasaら[25]によって行われた「ASDを有する若年者の不安に対する治療」に関するsystematic reviewによると，薬物療法としてはcitalopramとbuspironeの有効性が示されているものの，いずれもopen label trialでありエビデンスレベルは十分とはいえない。非薬物治療として，これまで認知行動療法を用いた9つの臨床研究が報告されており(うち8つがRCT)，高機能ASDの71.4％で有効であったとされている。2013年8月にNational Institute for Health and Care Excellence (NICE)より出版された最新のNICE clinical guideline ('Autism : the management and support of children and young people on the autism spectrum')[12]においても，不安症状に対して認知行動療法が推奨されている。

4. 気分障害

ASDに併存する気分障害の有病率に関しては，主に気分症状の言明が可能な高機能群を対象にした研究がいくつか報告されている。Ghaziuddinら[8]は，8～51歳(平均15歳)のアスペルガー障害の児童および成人35人に半構造化面接を行い，うち13名(37％)がうつ病を併存し，年齢が高いほどその合併率が高いことを報告している。また，並木ら[19]の行った高機能ASD 386名(平均年齢11.1±7.6歳)を対象にした気分障害の併存に関する横断調査によると，41名に気分障害(気分変調障害17名，大うつ病性障害24名)の併存が認められ，年齢が上がるほどその有病率が高かった。年齢が上がるにつれてうつ病性障害の有病率が高くなる要因の1つとして，山下[29]は，高機能ASDにおけるうつ病発症に関する心理社会的側面について言及し，ASDの認知行動特性を背景にした否定的体験の蓄積から社会生活上での困難さの気づきが増し，自己評価の低下や混乱を引き起こすことがうつ病発症の準備状況となりうると考察している。Munesueら[18]は，精神科外来受診中の青年期の高機能ASD 44名において，12名に双極性障害，4名に大うつ病性障害の併存を報告し，青年期ASDの状態像評価において，双極性障害を念頭に置くことの重要性を指摘している。次に，ASDにおける気分障害の臨床像と診断上の問題点について触れる。ASDを有する人では，たとえ高い言語的知能を有していても，自身の感情を認識し，悲哀感などのうつ病の中核症状を自発的に言語化することが困難なことは多い。また言語以外の表情や態度を介した感情表出も乏しいことが多いため，周囲からその変化が見逃される可能性もある。さらに，抑うつ症状が，常同行為の増加といった"(ASDの)主要徴候の増悪"に見える症状として出現する場合や，イライラ・自傷行為・攻撃性の増悪・catatonia (詳細は後述)というかたちで表出す

る場合もある。つまり，ASDを有する人では，気分障害の症状がASD症状にマスクされて他覚的に認識されにくいうえに，その症状の現れ方が，非定型的で，個々人によって独特なため，過小診断となる可能性がある。上記を念頭に，ASDの気分障害を評価する際は，「普段の行動特性との相違」をより意識することが重要となる[29]。すなわち，睡眠や食欲(食事量や体重)，排泄状況などの生理的側面の変化に加え，活動性の低下や動作の緩慢化の有無，こだわり行動や身辺自立行動の変化といった客観的事実に基づき状態像の把握に努める。これは，気分障害に限らずASDを有する人の状態像を把握するために重要な視点であり，特に知的障害を伴うASDにおける気分障害の存在を推測するために重要となる[1]。ASDの気分障害への介入については，まず心理社会的介入として，ASDの認知行動特性とその特性ゆえに生じやすいライフイベントや社会状況での困難さを，医療者を含めた周囲の人間が理解することが治療導入に不可欠である。そのうえで，他の併存症(不安障害など)の有無を含めた状態像を総合的に判断し，薬物治療の適応などを検討することになる。薬物治療に関しては，ASDに併存した気分障害に特化したガイドラインは存在しないため，通常のガイドラインに従い標的症状に対する薬剤選択を行うこととなる。基本的に少量より投与を開始し，ASDにおける双極性障害の高い合併率も念頭に置きながら，易怒性や衝動性の増悪の有無や他の併存症の変化も含めた慎重なモニタリングを心がけ，効果判定を行う必要がある。

5. 強迫性障害

強迫性障害における強迫症状と，ASDにおけるこだわりや常同行動との異同に関しては以前より議論されてきた。ASDの強迫関連行動は，"自我親和的"であるとみなされてきたが，近年，高機能ASDを有する人の中に，自我異和的な強迫症状を呈し自ら医療機関を受診するものが存在することも明らかになりつつある。Bejerotは，難治例の強迫性障害を呈する者の一部にASD特性を有する一群が存在することを受け，強迫性障害の下位分類として"autistic dimension"を提案し，発達障害の観点から強迫性障害の症例の状態像を検討することの重要性を提唱している[4]。ASDをベースに持つ強迫性障害の臨床上の特徴について，山下[30]は，"hoarding(溜め込み)"の存在を指摘している。介入に関しては，認知行動療法と抗うつ薬や非定型抗精神病薬を用いた薬物療法に関する報告が多数あり，これらの介入法の有効性が示唆されている一方で，介入の効果は限局的であるとする報告もある。ASDの強迫関連行動は，個々人の認知行動特性により多種多様であり，治療法の選択は個々の症例ごとに全体像を把握したうえでの検討が必要である。

6. 睡眠障害

睡眠障害は，ASDにおいて40～80％とほかの発達障害に比しても高率にみられ，主として入眠困難や睡眠維持の困難が報告されている[11]。睡眠障害は，常同行為の増加や社会的スキルの低下，イライラ・衝動性の増悪をもたらし，一見したところASD症状やAD/HD症状の増悪と捉えられる状態を引き起こすことがある[11]。このようなケースでは，衝動性の軽減などを目的に，非定型抗精神病薬やAD/HD治療薬が投薬されている例があるが，こうした対応は症状の改善がみられないばかりか，日中の眠気をもたらすなど睡眠の質のさらなる低下を招き，さらに状態像が悪化することがあるので注意を要する。したがって，ASDの状態像評価にあたり，日頃の睡眠状況を養育者から積極的に聴取し，睡眠障害が日中の行動になんらかの悪影響を及ぼしている可能性について注意深く検討する必要がある[12]。さらに，ASDを有する人に睡眠障害を認めた場合，これまでに述べたような精神科的併存症との関連性がないかについても検討を加える必要がある[12]。ASDを有する人およびその家族の包括的支援を目的に米国で設立されたAutism Treatment Network (ATN)では，睡眠状況の評価法やsleep kitを用いた睡

眠衛生への介入法などの情報を公開し，ASDの睡眠障害に関する指針を示しているので参照されたい[15]。また，薬物治療に関しては，ASDの睡眠障害の病態としてメラトニンに関連した異常が数多く報告されていることを受け，欧米を中心にメラトニンの有効性を示すRCTが多数報告されている[11]。

7. 自傷行為・癇癪・パニック

特に知的障害を有するASDを有する人において，時に著しい興奮やパニック，自傷行為がみられることがある。その要因は，同一性保持や感覚過敏を背景に，急な予定や状況の変化，本人の苦手とする感覚刺激などが誘因となる場合や合併する精神疾患の症状の一部として出現する場合などさまざまである[16]。誘因となる状況がはっきりしている場合は，それらの誘因を極力除くことが望ましいが，実際には周囲の人間にその誘因が十分に理解できない場合もあり，環境調整や行動介入だけでは対処困難な例も多い。そのため，非定型抗精神病薬を中心とした薬物治療もあわせて行われることも多い（薬物治療の詳細については他稿参照）。気分障害の項でも述べたように，標的症状以外からも多角的な評価を心掛け，興奮・パニック・自傷行為の背景にあるetiologyを極力明確にする姿勢が重要である。

8. カタトニア（Catatonia, catatonia-like deterioration）

ASDを有する人の主に思春期青年期において，動作が緩慢になり時に止まってしまう・繰り返し行動が増えて動作が先に進まない・他者からの促しなしには次の行動に移れないなどの現象が時にみられる。Wingら[28]は，これらの症状がカタトニア（catatonia）とみなせるとし，ASDとcatatoniaの間の行動特性上の類似点から両者に共通する病態の存在を指摘した。さらに，ASDのcatatoniaの基本症状として，i）運動と言葉の緩慢化，ii）活動を開始したり，完遂することの困難さ，iii）他者による身体的あるいは言語的な促しに依存することの増加，iv）受動性の増加と自発性低下の4項目を提唱した。また，catatoniaにしばしば伴う症状として，昼夜逆転，反復的儀式行動の増加，パーキンソン様症状，興奮，不安焦燥があるとしている[28]。ASDにみられるcatatoniaの特性として，高岡ら[23]は，典型的な昏迷へ至ることが少ないこと，身体的ないし言語的促しにより軽減すること，興奮が伴うことはあるが基本症状ではない点などをあげている。近年，Wingら[27]も，ASDにみられるcatatoniaが典型的症状を備えていない場合もあるとの理由から，catatonia-like deteriorationという表現を提唱している。Wingらによる有病率と発症年齢に関する報告によると，ASD診断を受けた初診患者506名のうち，30名（6%）がcatatoniaの診断基準を満たし，内訳として1～14歳（0/332：0%），15～19歳（12/65：17%），20～24歳（8/48：17%），25～29歳（3/19：16%），30～34歳（5/20：25%），35歳以上（2/23：9%）であり，思春期青年期に多いことが示されている[28]。発症時期については，9歳以下での発症はなく，10～19歳での発症が23名（76%）であり，10代で初発するケースが多い。また，catatoniaの診断基準を満たした30名の知的レベルはさまざまであり，過去の症例報告からもcatatoniaは知的レベルに関係なく生じることが示唆されている[5]。Catatonia出現の背景因子は，なんらかの外的要因（ストレス，急激な生活状況の変化など）による限局的反復行動の増悪や気分障害をはじめとする併存精神疾患の合併によるなどさまざまである[28]。Wingは，catatoniaの状態にある本人のつらさに共感を示し，家族の理解を促すとともに，活動しやすい環境作りや適切な言動面での促しを行うなどの心理社会的介入の重要性をあげている。また，症例数は少ないものの，高用量のロラゼパムや電気けいれん療法の有効性に関するエビデンスが蓄積しつつあり，特に重症例への治療手段として注目されつつある[5]。

精神科的併存症の早期発見・早期介入に向けて

以上のように，ASDでは多種多様な精神科的併存症が認められ，症例によっては複数存在する。また，ASDにおける併存症の独特な現れ方や各併存症が複雑に影響し合う可能性についても理解を深めることが重要であり，このことを強く意識したうえで，treatableな併存症を極力見逃さない姿勢が求められる。実際に併存症への介入を検討する際には，まず家族機能などの本人を取り巻く状況や日常生活上の適応度を考慮したうえで，中核症状・併存症双方の観点から包括的な評価を行う必要がある。なぜならば，各症例において，一番問題となっている併存症のみならず，その他の併存症の重畳がないかをスクリーニングすることで，主たる介入対象とする併存症出現の背景にあるetiologyがより明確になり，その症例にあったベストな介入法の検討が可能になるからである。NICE clinical guideline[12]においても，「ASDの臨床に関わるあらゆる専門家が，ASDにおける身体的・精神的併存症の評価，マネージメントに関するトレーニングを受け，併存症に対する適切な心理社会的治療または薬物治療が行われるべきである」と明記されている。ASDにおける併存症の重要性が認識されるにつれ，海外では2000年代後半から，ASDの精神科的併存症を包括的に評価する尺度の開発や臨床研究が数多く報告されている[17]。本邦においても，多職種間のスムーズな支援連携・薬物治療の適正化などに向け，併存症のスクリーニング・継続評価を包括的に行うツールの開発や人材育成，そして体制の構築が重要と考えられる。

文献

1) Adams D, Oliver C : The expression and assessment of emotions and internal states in individuals with severe or profound intellectual disabilities. Clin Psychol Rev 31 : 293–306, 2011
2) American Psychiatric Association : Diagnostic and statistical manual of mental disorders, 5th Edition. Washington DC, 2014
3) American Psychiatric Association : Diagnostic and statistical manual of mental disorders, 4th Edition, Text Revision. Washington DC, 2000
4) Bejerot S : An autistic dimension: a proposed subtype of obsessive-compulsive disorder. Autism 11 : 101–110, 2007
5) DeJong H, Bunton P, Hare DJ : A systematic review of interventions used to treat catatonic symptoms in people with autistic spectrum disorders. J Autism Dev Disord 44 : 2127–2136, 2014
6) Doherty JL, Owen MJ : Genomic insights into the overlap between psychiatric disorders: implications for research and clinical practice. Genome Med 6 : 29, 2014
7) Drahota A, Wood JJ, Sze KM et al : Effects of cognitive behavioral therapy on daily living skills in children with high-functioning autism and concurrent anxiety disorders. J Autism Dev Disord 41 : 257–265, 2011
8) Ghaziuddin M, Weidmer-Mikhail E, Ghaziuddin N : Comorbidity of Asperger syndrome: a preliminary report. J Intellect Disabil Res 42 : 279–283, 1998
9) Gjevik E, Sandstad B, Andreassen OA et al : Exploring the agreement between questionnaire information and DSM-IV diagnoses of comorbid psychopathology in children with autism spectrum disorders. Autism, 2014 (in Press)
10) Hofvander B, Delorme R, Chaste P et al : Psychiatric and psychosocial problems in adults with normal-intelligence autism spectrum disorders. BMC Psychiatry 9 : 35, 2009
11) Johnson KP, Malow BA : Sleep in children with autism spectrum disorders. Curr Neurol Neurosci Rep 8 : 155–161, 2008
12) Kendall T, Megnin-Viggars O, Gould N et al : Management of autism in children and young people: summary of NICE and SCIE guidance. BMJ 347 : f4865, 2013
13) Lai MC, Lombardo MV, Baron-Cohen S : Autism. Lancet 383 : 896–910, 2014
14) Leyfer OT, Folstein SE, Bacalman S et al : Comorbid psychiatric disorders in children with autism: interview development and rates of disorders. J Autism Dev Disord 36 : 849–861, 2006
15) Malow BA, Byars K, Johnson K et al : A practice pathway for the identification, evaluation, and

management of insomnia in children and adolescents with autism spectrum disorders. Pediatrics 130 : 106–124, 2012
16) Matson JL, Sipes M, Fodstad JC et al : Issues in the management of challenging behaviours of adults with autism spectrum disorder. CNS Drugs 25 : 597–606, 2011
17) Matson JL, Williams LW : The making of a field: the development of comorbid psychopathology research for persons with intellectual disabilities and autism. Res Dev Disabil 35 : 234–238, 2014
18) Munesue T, Ono Y, Mutoh K et al : High prevalence of bipolar disorder comorbidity in adolescents and young adults with high-functioning autism spectrum disorder: a preliminary study of 44 outpatients. J Affect Disord 111 : 170–175, 2008
19) 並木典子，杉山登志郎，明翫光宣：高機能広汎性発達障害にみられる気分障害に関する臨床的研究．小児の精神と神経 46：257–263，2006
20) 野村健介：自閉症スペクトラム障害に併存するAD/HDにいかに対応するか．臨床精神薬理 17：1257–1264，2014
21) 岡田　俊：精神病症状を伴う思春期・成人期の自閉症スペクトラム障害の診断と介入．臨床精神薬理 16：345–355，2013
22) Simonoff E, Pickles A, Charman T et al : Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. J Am Acad Child Adolesc Psychiatry 47 : 921–929, 2008
23) 高岡　健，関　正樹：自閉症スペクトラム障害のカタトニー様症状－その特徴と統合失調症との鑑別－．精神科治療学 25：1633–1637，2010
24) Taurines R, Schwenck C, Westerwald E et al : ADHD and autism: differential diagnosis or overlapping trait? A selective review. Atten Deficit Hyperactivity Disorder 4 : 115–139, 2012
25) Vasa RA, Carroll LM, Nozzolillo AA et al : A Systematic Review of Treatments for Anxiety in Youth with Autism Spectrum Disorders. J Autism Dev Disord, 2014 (in Press)
26) White SW, Oswald D, Ollendick T et al : Anxiety in children and adolescents with autism spectrum disorders. Clin Psychol Rev 29 : 216–229, 2009
27) Wing L, Shah A : A systematic examination of catatonia-like clinical pictures in autism spectrum disorders. Int Rev Neurobiol 72 : 21–39, 2006
28) Wing L, Shah A : Catatonia in autistic spectrum disorders. Br J Psychiatry 176 : 357–362, 2000
29) 山下　洋：気分障害と広汎性発達障害．臨床精神医学 37：1525–1533，2008
30) 山下陽子：広汎性発達障害を伴う強迫性障害の特徴についての研究．精神神経学雑誌 112：853–866，2010

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Default mode network in young male adults with autism spectrum disorder: relationship with autism spectrum traits

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Abstract

Go to:

Background

Autism spectrum traits are postulated to lie on a continuum that extends between individuals with autism and individuals with typical development (TD). Social cognition properties that are deeply associated with autism spectrum traits have been linked to functional connectivity between regions within the brain's default mode network (DMN). Previous studies have shown that the resting-state functional connectivities (rs-FCs) of DMN are low and show negative correlation with the level of autism spectrum traits in individuals with autism spectrum disorder (ASD). However, it is unclear whether individual differences of autism spectrum traits are associated with the strength of rs-FCs of DMN in participants including the general population.

Methods

Using the seed-based approach, we investigated the rs-FCs of DMN, particularly including the following two core regions of DMN: the anterior medial prefrontal cortex (aMPFC) and posterior cingulate cortex (PCC) in 19 young male adults with high-functioning ASD (mean age = 25.3 ± 6.9 years; autism-spectrum quotient (AQ) = 33.4 ± 4.2; full scale IQ (F-IQ) = 109.7 ± 12.4) compared with 21 age- and IQ-matched young male adults from the TD group (mean age = 24.8 ± 4.3 years; AQ = 18.6 ± 5.7; F-IQ = 109.5 ± 8.7). We also analyzed the correlation between the strength of rs-FCs and autism spectrum traits measured using AQ score.

Results

e strengths of rs-FCs from core regions of DMN were significantly lower in ASD participants than TD
ticipants. Under multiple regression analysis, the strengths of rs-FCs in brain areas from aMPFC seed showed
tive correlation with AQ scores in ASD participants and TD participants.

clusions

dings suggest that the strength of rs-FCs in DMN is associated with autism spectrum traits in the TD
on as well as patients with ASD, supporting the continuum view. The rs-FCs of DMN may be useful
ers for the objective identification of autism spectrum traits, regardless of ASD diagnosis.

ds: Autism spectrum disorder (ASD), Autism spectrum traits, Autism-spectrum quotient (AQ), Default
work (DMN), Resting-state functional connectivities (rs-FCs), Anterior medial prefrontal cortex
, Posterior cingulate cortex (PCC)

Go to:

nd

um disorder (ASD) is a complex neurodevelopmental disorder characterized by impaired social
and social interaction, and unusually restricted, repetitive behaviors and interests [1,2]. These
re postulated to lie on a continuum that extends between individuals with autism and individuals
lopment (TD) [3,4]. This continuum view suggests the possibility that autism spectrum traits are
igh levels in individuals with ASD but also at lower levels among individuals without ASD
m view shifts us away from merely categorical diagnosis towards the quantitative support of
ciated with autism spectrum traits of each individual regardless of ASD diagnosis. Taking
t into consideration necessitates the use of an instrument that can quantify autism spectrum
ation; such an instrument could also be used to define the broader autism phenotype [8,9].

utism spectrum traits, several instruments have been developed. The autism-spectrum
e is a useful instrument that was developed for identifying the extent of autistic
at adults of normal intelligence may have autism spectrum traits at various levels
dated measure of autism spectrum characteristics found within both the typical
with a diagnosis of autism [10,11].

e shown that individual differences in autism spectrum traits measured using AQ
nce of social cognition processing tasks such as self-focused attention, mind
nferring others' mental state in both a population with ASD and that with TD
lso demonstrate that autism spectrum traits measured using AQ are associated
rmalities in brain regions including the insula, inferior frontal gyrus, and
which are involved in social cognition processing in individuals with and
ber, these findings indicate that it is very important to evaluate the
he level of autism spectrum traits.

rocesses have been linked with cortical midline brain regions such as PCC
C), reflecting the high functional connectivities within the default mode
ividuals with TD, the functional connectivities of DMN are consistently
ed in a cognitively demanding, goal-oriented task [21]. On the other
engaged during social cognition processing tasks such as self-reference
rked overlap between brain regions of the DMN and regions of the
s of the DMN are strongly associated with the social cognition process

ith ASD have shown its lower functional connectivities in resting-
(rs-fMRI), using the approaches of both region of interest (ROI)
(ICA), than in individuals with TD [27-32]. In addition, these
een the strength of the resting-state functional connectivity (rs-FC)
ocial deficits in individuals with ASD. However, these studies
n the strength of rs-FCs of DMN and autism spectrum traits only
t of our knowledge, the individual differences in autism spectrum
ich may also be associated with the strength of rs-FCs of DMN in
evaluated.

The aims of this study were: (1) to clarify the rs-FCs of DMN in high-functioning young male adults with ASD by comparison with age- and IQ-matched young male adults with TD on the basis of the location of ROIs within DMN during rs-fMRI; and (2) to evaluate correlations between the strength of rs-FCs of DMN and autism spectrum traits measured using AQ scores in TD participants and ASD participants, respectively.

Methods

Go to:

Participants

Nineteen male individuals with high-functioning ASD were recruited by the Department of Neuropsychiatry at the University of Fukui Hospital, Japan, and the Department of Psychiatry and Neurobiology of the Kanazawa University Hospital, Japan. The authors (HK and TMu) diagnosed the participants on the basis of the criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [33] and standardized criteria taken from the Diagnostic Interview for Social and Communication Disorders (DISCO) [34]. The DISCO is reported to have good psychometric properties [35]. It also contains items on early development, and a section on activities of daily life, thereby giving the interviewer an idea of the individual's level of functioning in several different areas, not only social functioning and communication [35]. All participants were right-handed [36]. Twenty-one age-matched and intelligence quotient (IQ)-matched TD male participants were recruited from the local community. Individuals with a history of major medical or neurological illness, including epilepsy, significant head trauma, or a lifetime history of alcohol or drug dependence, were excluded from this study. They were screened to exclude individuals who had a first degree relative with an Axis I disorder, diagnosed on the basis of the DSM-IV criteria. IQ was assessed using the Wechsler Adult Intelligence Scale-III (WAIS-III) [37]. All the participants had full scale IQ (F-IQ) scores >85. There were no significant differences between the groups in terms of age, verbal IQ, performance IQ, and F-IQ (all $P > 0.5$). All the participants also completed the AQ questionnaire [10]. The protocol used for this study was approved by the ethics committee of the University of Fukui. After a complete explanation of the study, all the participants provided written, informed consent. Their mean age, handedness, IQ and AQ score are shown in Table 1.

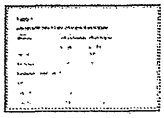

Table 1

Demographic data, IQ and AQ scores of participants

fMRI data acquisition

Functional images were acquired with T2*-weighted gradient-echo echo-planar imaging (EPI) sequence using a 3-T imager (Discovery MR 750; General Electric Medical Systems, Milwaukee, WI, USA) and a 32-channnel head coil. Two hundred and one volumes were acquired in each participant. Each volume consisted of 40 slices, with a thickness of 3.5 mm and a 0.5 mm gap to cover the entire brain. The time interval between two successive acquisitions of the same slice (repetition time, TR) was 2,300 ms, with an echo time (TE) of 30 ms and a flip angle (FA) of 81 degrees. The field of view (FOV) was 192 × 192 mm and the matrix size was 64 × 64, giving volume dimensions of 3 × 3 mm. The participants were instructed to close their eyes but stay awake and think of nothing in particular. A total of 201 volumes were acquired for a total imaging time of 7 min 42 s. The experiment was conducted at the Biomedical Imaging Research Center of the University of Fukui.

fMRI data analysis

Preprocessing

Data were analyzed using SPM8 software (Wellcome Department of Imaging Neuroscience, London, UK). After discarding the first five volumes, all volumes were realigned spatially to the mean volume, and the signal from each slice was realigned temporally to that obtained from the middle slice using sinc interpolation. The resliced volumes were normalized to the Montreal Neurological Institute (MNI) space with a voxel size of 2 × 2 × 2 mm using the EPI template of SPM8. The normalized images were spatially smoothed with a 6-mm Gaussian kernel.

Rs-fMRI datasets were processed using a toolkit of the Data Processing Assistant for Resting-State fMRI (DPARSF; http://www.restfmri.net) [38]. We conducted additional processing as follows: (1) removing the linear trend in the time series; and (2) performing temporally bandpass filtering (0.01-0.08 Hz) to reduce the effects of low-frequency drift and high-frequency noise [39,40]. To control the non-neural noise in the time series [41]; (3)

several sources of spurious variance, that is, six parameters from the rigid body correction of head motion, white matter signals, CSF signals, and global signals were removed from the data through linear regression [42].

Head movement parameters

Rs-FCs of DMN are significantly affected by the head motion of participants during fMRI scanning; that is, long-distance correlations are decreased by participant motion, whereas many short-distance correlations are increased [43-47]. To investigate the effect of head motion and motion artifacts in rs-FCs, the root mean square (RMS) of six movement parameters obtained in the realignment process (x-, y-, z translations and x-, y-, z rotations), mean frame-to-frame RMS motion [43] and frame-wise displacement (FD) [45] were calculated for each participant. There were no significant differences in RMS (P values ranged from 0.17 to 0.70), mean frame-to-frame RMS motion (P value was 0.11) and FD (P value was 0.14) between the groups. In addition, there is no significant relationship between AQ scores and the six RMS head movement parameters (P values ranged from 0.10 to 0.78).

Definition of ROIs

To clarify the rs-FCs of DMN in the present study, we defined the regions in the anterior MPFC (aMPFC) and PCC as ROIs. The ROI coordinates were selected from the DMN meta-analysis [48]. The seed regions of the aMPFC and PCC comprise core seeds within the functional connectivity of DMN, and their widespread connectivities are supported by connectional anatomy studies [48-50]. Two spherical ROIs of 8 mm radius centered at a coordinate listed in Table 2 were drawn for each participant in line.

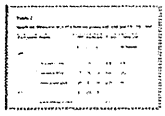

Table 2

Significant differences in rs-FCs between groups with ASD and TD (TD >ASD)

Rs-FC analysis

After the processing of rs-fMRI data, we used the predefined seed regions for voxel-wise rs-FC analyses using the DPARSF toolbox. The mean time course of all voxels in each seed ROI was used to calculate voxel-wise linear correlations (Pearson's correlation) in the whole brain during the rs-fMRI period. Individuals' r values were normalized to z values using Fisher's z transformation. At the group level, each image pertaining to z values reflecting a correlation between the seed ROI and each voxel of the brain was entered into a random effect two-sample t-test to identify the whole-brain regions showing significant differences between the groups with ASD and TD. In seed-based rs-FC analyses, global time series, computed across all brain voxels, along with six motion parameters, were used as additional covariates to remove confounding effects of physiologic noise and participant movement. For the presentation purpose, rs-FCs from the aMPFC and PCC seed ROIs are shown separately for each group at the threshold of $P = 0.05$ with a family wise error correction (Figure 1). Results were corrected between group comparisons, set at $P = 0.001$, uncorrected at peak level, and $P = 0.05$ with cluster level.

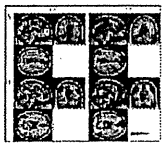

Figure 1

Results of rs-FCs from the aMPFC or PCC seed for each group. (A) Rs-FCs from the aMPFC seed ROI are shown for each group. **(B)** Rs-FCs from the PCC seed ROI are shown for each group. The statistical threshold for both results was set at $P = 0.05$ ...

Relationships among rs-FCs of group differences with AQ or IQ

To confirm the relationship between the significant difference in strength of rs-FCs and autism spectrum traits or IQ, we calculated correlations between AQ scores, F-IQ and the Z values, which were extracted from the regions showing the strength of rs-FCs of significant group differences (Spearman's rank order correlation coefficients; the statistical threshold was set at $P = 0.01$).

Multiple regression analysis among the strength of rs-FC with AQ, IQ, or age

To investigate the relationships among the strength of rs-FC, autism spectrum traits, IQ, or age across each group, we performed additional analyses of nine independent variables in a multiple regression analysis in SPM8, AQ total scores, F-IQ, age, and RMS of six movement parameters as covariates. The statistical threshold for contrasts

was P <0.001 uncorrected for height and cluster P <0.05 corrected for multiple comparisons. In addition, we tested whether the five AQ subscale scores would also show correlations with the brain regions and we observed correlations in each group.

Results

Go to:

Differences in the strength of rs-FCs in DMN between groups

Rs-FCs from the aMPFC and PCC seed regions were distributed in the medial parts of the brain (Figure 1). In the ASD group compared with the TD group, substantially smaller areas were functionally connected with these seed regions.

In the ROIs within the DMN, significant differences in the strength of rs-FCs from the aMPFC seed were observed in the paracentral lobuli and middle frontal gyrus (MFG) between the two groups (Table 2, Figure 2). A significant difference in rs-FCs from the PCC seed was observed in the MPFC between the groups (Table 2, Figure 3). The mean correlation coefficient (Fisher z-transformed) for each group is shown in Figure 2 and Figure 3. The strengths of all of these rs-FCs were lower in the ASD group compared with the TD group. Individuals with ASD showed no significantly higher strength of rs-FCs from the seed regions compared with the TD group.

Figure 2

Results of rs-FCs from the aMPFC seed ROI between groups. (A) Comparison of rs-FCs from the aMPFC seed ROI between groups. There were significant clusters in the paracentral lobuli (left) and middle frontal gyrus (right). Detailed information on these ...

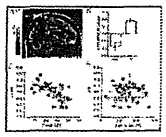

Figure 3

Results of rs-FCs from the PCC seed ROI between groups. (A) Comparison of rs-FCs from the PCC seed ROI between groups. There was a significant difference in the medial prefrontal cortex. Detailed information on the cluster is shown in Table 2 ...

Relationship between the strength of rs-FCs of group differences and AQ or IQ

In the ASD group, there were no significant correlations between either the strength of rs-FCs and F-IQ or AQ total score (Figure 2; Figure 3, P >0.01). In the TD group, there were also no significant correlations between either the strength of rs-FCs and F-IQ or AQ total score (Figure 2; Figure 3, P >0.01).

Relationship with AQ or IQ in the multiple regression analysis

In the ASD group, AQ total scores were significantly negatively correlated with the strength of rs-FC in aMPFC with MFG and cerebellum (Table 3; Figure 4, P <0.01). We also found that two AQ subscale scores (communication scores and attention switching scores) also significantly negatively correlated with the strength of rs-FCs in aMPFC with MFG and cerebellum (P <0.05). In the TD group, AQ total scores were significantly negatively correlated with the strength of rs-FC in aMPFC with superior temporal gyrus (STG) and MTG (Table 3; Figure 4, P <0.01). We also found that three AQ subscale scores (social skill scores, communication scores, and attention switching scores) also significantly negatively correlated with the strength of rs-FCs in aMPFC with STG and MTG (P <0.01).

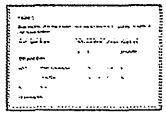

Table 3

Brain regions showing negative correlations between AQ and the strength of rs-FCs in multiple regression analysis

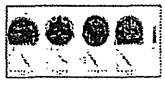

Figure 4

Brain regions showing negative correlations between AQ and the strength of rs-FCs from aMPFC seed in each group. Brain regions showing negative correlations between AQ and strength of rs-FCs from aMPFC seed in multiple regression analysis. The statistical ...

There were no significant correlations between the strength of rs-FCs and each participant's F-IQ in all the participants, in the ASD group or in the TD group, in the multiple regression analysis ($P > 0.01$).

Relationship with age in the multiple regression analysis

In the TD group, age was significantly positively correlated with the strength of rs-FCs in the aMPFC with MTG and PCC with cingulate gyrus (Table 4; Figure 5). We found no significant correlations between age and the strength of rs-FCs of DMN, in the ASD group or all the participants.

Table 4

Brain regions showing correlations between age and the strength of rs-FCs in multiple regression analysis

Figure 5

Brain regions showing positive correlations between age and the strength of rs-FCs from seed regions in TD participants. Brain regions showing positive correlations between age and the strength of rs-FCs from seed regions in multiple regression analysis. ...

Discussion

Go to:

We found that young male adults with high-functioning ASD display lower rs-FCs between two seeds (aMPFC and PCC) of DMN and other brain regions In addition, we found that autism spectrum traits measured using the AQ score are associated with the strength of rs-FCs of DMN that contain brain regions relevant to social cognition processing, in each TD participants and ASD participants, respectively. These results complement previous studies [26,29,31], suggesting that the strengths of rs-FCs of DMN are associated with autistic spectrum traits of social cognition processing in ASD participants. In addition, our results showed that this association between the strength of rs-FCs of DMN and autistic spectrum traits also exists not only in ASD participants but also in TD participants. These findings suggest that the strength of rs-FCs of DMN may underlie some of the autism spectrum traits, regardless of ASD diagnosis.

Difference in functional connectivities of DMN between ASD and TD groups

Our results mostly agree with those of other studies of rs-FCs of DMN [27-32] that demonstrated lower rs-FCs of DMN in ASD. However, as for MPFC, the regions showing lower functional connectivities in previous studies are not always in agreement with those found in this study [27-30,32]. Differences in approach (seed-based or ICA) might have made direct comparisons between results somewhat challenging [51]. Andrews-Hanna *et al.* [49] demonstrated that the aMPFC of DMN is associated with social cognition processes including judgments or remembering trait adjectives about themselves compared with other people, whereas the dorsal medial prefrontal cortex (dMPFC) of DMN is associated with social cognition processes including self-referential judgments about their present situation or mental states. These findings taken together with our findings suggest that rs-FCs in brain regions including both aMPFC and dMPFC are associated with autism spectrum traits associated with processes of basic social cognition of self and others in individuals with ASD.

DMN associated with autism spectrum traits

In recent studies of rs-FCs of DMN in ASD, correlations have been investigated between autism spectrum traits and functional connectivities within brain areas such as the precuneus [27], MPFC [27,29,32], anterior cingulate cortex [27], and superior frontal gyrus [31]. However, most of these studies analyzed these correlations in only ASD participants. In general, these studies suggest negative correlation between the strength of rs-FCs of DMN and autism spectrum traits in individuals with ASD.

In the current findings, the strength of rs-FCs in brain areas from aMPFC seed showed negative correlations with AQ total score not only in ASD participants but also in TD participants in the multiple regression analysis, although these areas from aMPFC seed that showed negative correlations with AQ total scores in two groups were different from each other (Table 3). Moreover, among AQ subscale scores, communication scores and attention switching scores were related to the strength of rs-FCs of DMN in the ASD group. On the other hand, social skill scores, communication scores, and attention switching scores were related to the strength of rs-FCs of

DMN in the TD group. Our findings suggest that the strength of rs-FCs of DMN might underlie the level of autism spectrum traits in participants without ASD diagnosis or with subthreshold autism spectrum traits, supporting the continuum view. In addition, considering the results of the multiple regression analysis using AQ subscale scores, the nature of autism spectrum traits, which affects the strength of rs-FCs of DMN in aMPFC seed, might be different in each group and the function of DMN might not always be the same between ASD and TD groups.

Age-related changes in functional connectivities of DMN

Particularly interesting from our viewpoint is the lack of consensus regarding the strength of rs-FC aspects of age variation with ASD. In relation to age-related changes in DMN in ASD, few studies have examined age correlates of functional connectivities by rs-fMRI. To the best of our knowledge, only one rs-fMRI study has examined the functional connectivities in children with ASD compared with age- and IQ-matched children with TD [52]. The previous study showed higher rs-FCs of DMN in PCC seeds in children with ASD than in children with TD [52], but we found that lower rs-FCs of DMN in PCC seeds in the ASD group and a relationship between rs-FCs of DMN in PCC seeds and age in the TD group. We speculate that the age-related changes in the functional connectivities of DMN in ASD and TD may be linked to differences in neurodevelopmental mechanisms in childhood and numerous variables including point of development. Future studies are required to explore the variation of rs-FCs of DMN with age for individuals with ASD.

Future directions

First, the size of each group in this study may be relatively too small to demonstrate a relationship between the various levels of autism spectrum traits and the strength of rs-FCs of DMN. Second, we defined the seed regions for rs-FC analyses on the basis of the location of ROIs within the DMN in accordance with a previous study. Although the seed-based analysis in the present research makes it possible to determine rs-FC precisely, this analysis did not reveal information about intrinsically connected networks and their interactions [51]. Future study is necessary to replicate these findings, using the ICA approach for exploring information about intrinsically connected networks. Third, we included global signal regression in generating the FC map. However, it is a quite controversial issue whether global signal regression changes resting-state correlations and produces negative correlations [53]. Thus, the findings used in the present study are not definitive, and future study is necessary to compare the results with confound regression strategies. Finally, our participants were only young male adults with high-functioning ASD. Future study is needed to clarify rs-FCs in both males and females, children with ASD, and ASD individuals without high-functioning. These additional researches will help provide more complete pictures that may clarify the etiology of ASD.

Conclusions

Go to:

Young male adults with high-functioning ASD showed lower rs-FCs of DMN compared with age- and IQ-matched young male adults with TD. Moreover, the strength of rs-FCs of DMN was associated with autism spectrum traits in each ASD and TD group, regardless of ASD diagnosis. We propose that the strength of rs-FCs of DMN might underlie the level of autism spectrum traits and might be one of the potential biomarkers for the objective identification of the level of autism spectrum traits, regardless of ASD diagnosis.

Abbreviations

Go to:

AMPFC: Anterior medial prefrontal cortex; AQ: Autism-spectrum quotient; ASD: Autism spectrum disorder; DMN: Default mode network; DMPFC: Dorsal medial prefrontal cortex; IQ: Intelligence quotient; PCC: Posterior cingulate cortex; Rs-FC: Resting-state functional connectivities; TD: Typical development.

Competing interests

Go to:

The authors declare that they have no competing interests.

Authors' contributions

Go to:

MJ was involved in conducting the experiment, analyzing and interpreting data, and drafting the article. HK was involved in recruiting the participants, diagnosing the participants with ASD, conducting the experiment, analyzing and interpreting data, and drafting the article. DNS, TM (fifth author), and KI were involved in

recruiting the participants and conducting the experiment. MI was involved in recruiting the participants, interpreting data, and drafting the article. TM (eighth author) was involved in recruiting the participants and diagnosing the participants with ASD. MA, SA, AT, YW, NS, and HO were involved in interpreting the data. TI was involved in designing, analyzing and interpreting data, and drafting the article. All the authors have read and approved the final manuscript.

Acknowledgments

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References

Go to:

1. Lai M-C, Lombardo MV, Chakrabarti B, Baron-Cohen S. Subgrouping the autism "spectrum": reflections on DSM-5. PLoS Biol. 2013;11:e1001544. doi: 10.1371/journal.pbio.1001544. [PMC free article] [PubMed] [Cross Ref]
2. Autism and Developmental Disabilities Monitoring Network Surveillance Year 2008 Principal Investigators; Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders -- Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2008. MMWR Surveill Summ. 2012;61:1–19. [PubMed]
3. Frith U. Autism and Asperger Syndrome. Cambridge: Cambridge University Press; 1991.
4. Baron-Cohen S. Mindblindness: An Essay on Autism and Theory of Mind. Cambridge, MA: MIT Press; 1997.
5. Constantino JN, Hudziak JJ, Todd RD. Deficits in reciprocal social behavior in male twins: evidence for a genetically independent domain of psychopathology. J Am Acad Child Adolesc Psychiatry. 2003;42:458–467. doi: 10.1097/01.CHI.0000046811.95464.21. [PubMed] [Cross Ref]
6. Skuse DH, Mandy W, Steer C, Miller LL, Goodman R, Lawrence K, Emond A, Golding J. Social communication competence and functional adaptation in a general population of children: preliminary evidence for sex-by-verbal IQ differential risk. J Am Acad Child Adolesc Psychiatry. 2009;48:128–137. doi: 10.1097/CHI.0b013e31819176b8. [PubMed] [Cross Ref]
7. Bölte S, Westerwald E, Holtmann M, Freitag C, Poustka F. Autistic traits and autism spectrum disorders: The clinical validity of two measures presuming a continuum of social communication skills. J Autism Dev Disord. 2011;41:66–72. doi: 10.1007/s10803-010-1024-9. [PMC free article] [PubMed] [Cross Ref]
8. Wheelwright S, Auyeung B, Allison C, Baron-Cohen S. Defining the broader, medium and narrow autism phenotype among parents using the Autism Spectrum Quotient (AQ) Mol Autism. 2010;1:10. doi: 10.1186/2040-2392-1-10. [PMC free article] [PubMed] [Cross Ref]
9. Happé F, Ronald A, Plomin R. Time to give up on a single explanation for autism. Nat Neurosci. 2006;9:1218–1220. doi: 10.1038/nn1770. [PubMed] [Cross Ref]
10. Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E. The autism-spectrum quotient (AQ): Evidence from asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. J Autism Dev Disord. 2001;31:5–17. doi: 10.1023/A:1005653411471. [PubMed] [Cross Ref]
11. Woodbury-Smith MR, Robinson J, Wheelwright S, Baron-Cohen S. Screening Adults for Asperger Syndrome Using the AQ: A Preliminary Study of its Diagnostic Validity in Clinical Practice. J Autism Dev Disord. 2005;35:331–335. doi: 10.1007/s10803-005-3300-7. [PubMed] [Cross Ref]
12. Lombardo MV, Barnes JL, Wheelwright SJ, Baron-Cohen S. Self-referential cognition and empathy in autism. PLoS One. 2007;2:e883. doi: 10.1371/journal.pone.0000883. [PMC free article] [PubMed] [Cross Ref]
13. Golan O, Baron-Cohen S, Hill JJ, Rutherford MD. The "reading the mind in the voice" test-revised: A study of complex emotion recognition in adults with and without autism spectrum conditions. J Autism Dev Disord. 2007;37:1096–1106. doi: 10.1007/s10803-006-0252-5. [PubMed] [Cross Ref]

14. Komeda H, Kosaka H, Saito DN, Inohara K, Munesue T, Ishitobi M, Sato M, Okazawa H. Episodic memory retrieval for story characters in high-functioning autism. Mol Autism. 2013;4:20. doi: 10.1186/2040-2392-4-20. [PMC free article] [PubMed] [Cross Ref]
15. Baron-Cohen S, Wheelwright S, Hill J, Raste Y, Plumb I. The " Reading the Mind in the Eyes " Test Revised Version: A Study with Normal Adults, and Adults with Asperger Syndrome or High-functioning Autism. J Child Psychol Psychiatry. 2001;42:241–251. doi: 10.1111/1469-7610.00715. [PubMed] [Cross Ref]
16. Kosaka H, Omori M, Munesue T, Ishitobi M, Matsumura Y, Takahashi T, Narita K, Murata T, Saito DN, Uchiyama H. Smaller insula and inferior frontal volumes in young adults with pervasive developmental disorders. Neuroimage. 2010;50:1357–1363. doi: 10.1016/j.neuroimage.2010.01.085. [PubMed] [Cross Ref]
17. Ishitobi M, Kosaka H, Omori M, Matsumura Y, Munesue T, Mizukami K, Shimoyama T, Murata T, Sadato N, Okazawa H. Differential amygdala response to lower face in patients with autistic spectrum disorders: An fMRI study. Res Autism Spectr Disord. 2011;5:910–919. doi: 10.1016/j.rasd.2010.10.005. [Cross Ref]
18. Morita T, Kosaka H, Saito DN, Ishitobi M, Munesue T, Itakura S, Omori M, Okazawa H, Wada Y, Sadato N. Emotional responses associated with self-face processing in individuals with autism spectrum disorders: An fMRI study. Soc Neurosci. 2012;7:223–239. doi: 10.1080/17470919.2011.598945. [PubMed] [Cross Ref]
19. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci U S A. 2003;100:253–258. doi: 10.1073/pnas.0135058100. [PMC free article] [PubMed] [Cross Ref]
20. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci U S A. 2001;98:676–682. doi: 10.1073/pnas.98.2.676. [PMC free article] [PubMed] [Cross Ref]
21. Raichle ME, Snyder AZ. A default mode of brain function: A brief history of an evolving idea. Neuroimage. 2007;37:1083–1090. doi: 10.1016/j.neuroimage.2007.02.041. [PubMed] [Cross Ref]
22. Schilbach L, Eickhoff SB, Rotarska-Jagiela A, Fink GR, Vogeley K. Minds at rest? Social cognition as the default mode of cognizing and its putative relationship to the "default system" of the brain. Conscious Cogn. 2008;17:457–467. doi: 10.1016/j.concog.2008.03.013. [PubMed] [Cross Ref]
23. Amodio DM, Frith CD. Meeting of minds: the medial frontal cortex and social cognition. Nat Rev Neurosci. 2006;7:268–277. doi: 10.1038/nrn1884. [PubMed] [Cross Ref]
24. Gilbert SJ, Williamson IDM, Dumontheil I, Simons JS, Frith CD, Burgess PW. Distinct regions of medial rostral prefrontal cortex supporting social and nonsocial functions. Soc Cogn Affect Neurosci. 2007;2:217–226. doi: 10.1093/scan/nsm014. [PMC free article] [PubMed] [Cross Ref]
25. Buckner RL, Andrews–Hanna JR, Schacter DL. The brain's default network. Ann N Y Acad Sci. 2008;1124:1–38. doi: 10.1196/annals.1440.011. [PubMed] [Cross Ref]
26. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci. 2011;15:483–506. doi: 10.1016/j.tics.2011.08.003. [PubMed] [Cross Ref]
27. Assaf M, Jagannathan K, Calhoun V. Abnormal functional connectivity of default mode sub-networks in autism spectrum disorder patients. Neuroimage. 2010;53:247–256. doi: 10.1016/j.neuroimage.2010.05.067. [PMC free article] [PubMed] [Cross Ref]
28. Kennedy DP, Courchesne E. Functional abnormalities of the default network during self-and other-reflection in autism. Soc Cogn Affect Neurosci. 2008;3:177–190. doi: 10.1093/scan/nsn011. [PMC free article] [PubMed] [Cross Ref]
29. Monk C, Peltier S, Wiggins J, Weng S. Abnormalities of intrinsic functional connectivity in autism spectrum disorders. Neuroimage. 2009;47:764–772. doi: 10.1016/j.neuroimage.2009.04.069. [PMC free article] [PubMed] [Cross Ref]
30. Kennedy DP, Redcay E, Courchesne E. Failing to deactivate: resting functional abnormalities in autism. Proc Natl Acad Sci U S A. 2006;103:8275–8280. doi: 10.1073/pnas.0600674103. [PMC free article] [PubMed] [Cross Ref]
31. Weng S, Wiggins J, Peltier S, Carrasco M. Alterations of resting state functional connectivity in the default network in adolescents with autism spectrum disorders. Brain Res. 2010;1313:202–214. [PMC free article] [PubMed]

32. Von Dem Hagen EA H, Stoyanova RS, Baron-Cohen S, Calder AJ. Reduced functional connectivity within and between "social" resting state networks in autism spectrum conditions. Soc Cogn Affect Neurosci. 2013;8:694–701. doi: 10.1093/scan/nss053. [PMC free article] [PubMed] [Cross Ref]
33. Association AP. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR®. Arlington, VA: American Psychiatric Publishing; 2000.
34. Nygren G, Hagberg B, Billstedt E, Skoglund A, Gillberg C, Johansson M. The Swedish version of the Diagnostic Interview for Social and Communication Disorders (DISCO-10) Psychometric properties J Autism Dev Disord. 2009;39:730–741. doi: 10.1007/s10803-008-0678-z. [PubMed] [Cross Ref]
35. Wing L, Leekam SR, Libby SJ, Gould J, Larcombe M. The Diagnostic Interview for Social and Communication Disorders: background, inter-rater reliability and clinical use. J Child Psychol Psychiatry. 2002;43:307–325. doi: 10.1111/1469-7610.00023. [PubMed] [Cross Ref]
36. Oldfield RC. The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia. 1971;9:97–113. doi: 10.1016/0028-3932(71)90067-4. [PubMed] [Cross Ref]
37. Wechsler D. WAIS-III: Wechsler Adult Intelligence Scale. San Antonio, TX: Psychological Corporation; 1997.
38. Chao-Gan Y, Yu-Feng Z. DPARSF: A MATLAB Toolbox for "Pipeline" Data Analysis of Resting-State fMRI. Front Syst Neurosci. 2010;4:1–7. [PMC free article] [PubMed]
39. Biswal B, Zerrin Yetkin F, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar mri. Magn Reson Med. 1995;34:537–541. doi: 10.1002/mrm.1910340409. [PubMed] [Cross Ref]
40. Lowe MJ, Mock BJ, Sorenson JA. Functional Connectivity in Single and Multislice Echoplanar Imaging Using Resting-State Fluctuations. Neuroimage. 1998;7:119–132. doi: 10.1006/nimg.1997.0315. [PubMed] [Cross Ref]
41. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A. 2005;102:9673–9678. doi: 10.1073/pnas.0504136102. [PMC free article] [PubMed] [Cross Ref]
42. Satterthwaite TD, Elliott MA, Gerraty RT, Ruparel K, Loughead J, Calkins ME, Eickhoff SB, Hakonarson H, Gur RC, Gur RE, Wolf DH. An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. Neuroimage. 2013;64:240–256. [PMC free article] [PubMed]
43. Van Dijk KR A, Sabuncu MR, Buckner RL. The influence of head motion on intrinsic functional connectivity MRI. Neuroimage. 2012;59:431–438. doi: 10.1016/j.neuroimage.2011.07.044. [PMC free article] [PubMed] [Cross Ref]
44. Müller R, Shih P, Keehn B. Underconnected, but how? A survey of functional connectivity MRI studies in autism spectrum disorders. Cereb Cortex. 2011;21:2233–2243. doi: 10.1093/cercor/bhq296. [PMC free article] [PubMed] [Cross Ref]
45. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage. 2012;59:2142–2154. doi: 10.1016/j.neuroimage.2011.10.018. [PMC free article] [PubMed] [Cross Ref]
46. Satterthwaite TD, Wolf DH, Loughead J, Ruparel K, Elliott MA, Hakonarson H, Gur RC, Gur RE. Impact of in-scanner head motion on multiple measures of functional connectivity: relevance for studies of neurodevelopment in youth. Neuroimage. 2012;60:623–632. doi: 10.1016/j.neuroimage.2011.12.063. [PMC free article] [PubMed] [Cross Ref]
47. Deen B, Pelphrey K. Perspective: Brain scans need a rethink. Nature. 2012;491:S20. doi: 10.1038/491S20a. [PubMed] [Cross Ref]
48. Buckner RL, Sepulcre J, Talukdar T, Krienen FM, Liu H, Hedden T, Andrews-Hanna JR, Sperling RA, Johnson KA. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. J Neurosci. 2009;29:1860–1873. doi: 10.1523/JNEUROSCI.5062-08.2009. [PMC free article] [PubMed] [Cross Ref]
49. Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, Buckner RL. Functional-anatomic fractionation of the brain's default network. Neuron. 2010;65:550–562. doi: 10.1016/j.neuron.2010.02.005. [PMC free article] [PubMed] [Cross Ref]
50. Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, Sporns O. Mapping the structural core of human cerebral cortex. PLoS Biol. 2008;6:e159. doi: 10.1371/journal.pbio.0060159. [PMC free article] [PubMed] [Cross Ref]

51. Joel SE, Caffo BS, van Zijl PCM, Pekar JJ. On the relationship between seed-based and ICA-based measures of functional connectivity. Magn Reson Med. 2011;66:644–657. doi: 10.1002/mrm.22818. [PMC free article] [PubMed] [Cross Ref]
52. Lynch CJ, Uddin LQ, Supekar K, Khouzam A, Phillips J, Menon V. Default mode network in childhood autism: posteromedial cortex heterogeneity and relationship with social deficits. Biol Psychiatry. 2013;74:212–219. doi: 10.1016/j.biopsych.2012.12.013. [PMC free article] [PubMed] [Cross Ref]
53. Murphy K, Birn RM, Handwerker DA, Jones TB, Bandettini PA. The impact of global signal regression on resting state correlations: Are anti-correlated networks introduced? Neuroimage. 2009;44:893–905. doi: 10.1016/j.neuroimage.2008.09.036. [PMC free article] [PubMed] [Cross Ref]

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Distinguishing between autism spectrum disorder and attention deficit hyperactivity disorder by using behavioral checklists, cognitive assessments, and neuropsychological test battery

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ABSTRACT

Children with attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) share many common symptoms, including attention deficit, behavioral problems, and difficulties with social skills. The aim of this study was to distinguish between ASD and ADHD by identifying the characteristic features of both the disorders, by using multidimensional assessments, including screening behavioral checklists, cognitive assessments, and comprehensive neurological battery. After screening for comorbid disorders, we carefully selected age-, sex-, IQ-, and socio-economic status-matched children with typical development (TD). In the Wechsler Intelligence Scale for children, a lower score was observed for the ASD group than for the TD group in Picture concept, which is a subscale of perceptual reasoning. A lower score was shown by the ADHD group than by the TD group in the spatial working memory test in the Cambridge Neuropsychological Test Automated Battery (CANTAB®). Although ASD and ADHD have many similar symptoms, they can be differentiated by focusing on the behavioral and cognitive characteristics of executive function.

1. Introduction

Children with attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) have many common symptoms (Matson and Nebel-Schwalm, 2007), including attention deficit, behavioral problems, and difficulties with social skills. These various overlapping symptoms often complicate a differential diagnosis. Moreover, children diagnosed with ADHD likely show some autistic symptoms and vice versa, which presents a major problem when treating children and adolescents with developmental disorders. Because misdiagnosis leads to misunderstanding of patient symptoms and inadequate or inappropriate treatment; hence, it is important to understand the common and unique symptoms of these disorders, and the assessments that are the most useful in allowing clinicians to distinguish between two disorders.

Executive function (EF) is an overarching term when referring to mental control processes that enable physical, cognitive, and emotional self-control, which are necessary to maintain effective goal-directed behavior. EF generally includes response inhibition, working memory, cognitive flexibility, planning, and fluency. Moreover, they involve multiple distributed neural networks in the thalamus, basal ganglia, and prefrontal cortex. In particular, the prefrontal areas of the frontal lobe are important regions for performing EFs and complex cognitive processes (Alvarez and Emory, 2006). Many studies have suggested that the brain regions that are important for EF are those affected by ASD (Ozonoff et al., 2004; Lopez et al., 2005; Goldberg et al., 2005) and ADHD

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