関が連携して支援したことを報告している。

2. 本調査における外来初診患者の外来におけるサービス体制はどのようなものが求められるか

前項ですでに述べたように，現実の困難と精神症状はどちらが原因であるとは言いがたく絡み合っているので，外来での見立てと適切な医学的治療が基盤にあることが必須である。精神障害であるからには，むろん生活支援だけでは生活の上での困難は解消しないと思われる。言いたいことは，単純に福祉サービスを充実させることで解決できるわけではなく，外来機能の中に「ワンストップ・ショッピング」といえる支援機能があり，複合的な困難のある人をしばらくは抱えることができること，そしてある程度改善してきて，もしくは問題が整理されてきて初めて，通常の外来治療と福祉サービスへと切り離していくことが可能になるだろうということである。

相談支援事業をはじめとするケアマネジメント機能を厚生労働省は充実させようとしているし，以前に比べれば就労支援にしても生活支援にしても，地域の社会資源がはるかに増えていることは事実である。しかし余力のない人たちは違う場所に行っていろいろな支援を使っていくような力を持たない。そもそもどのような支援が必要か，本人には全く見えていないことも多い。

しかしそうした支援システムを外来機能の中に組み込むことは，今の医療経済の中では容易ではない。精神科のしっかりした経験を有し，かつ生活支援の力を持った専門家をどうしたら外来の中で抱えていくことができるだろうか。こうした機能を考えるとすぐに職種としてはソーシャルワーカーを思い浮かべることが多いと思うが，複雑な心的問題があったり，自立生活技能の課題を抱えていたり，慢性疾患の合併があったりするので，多職種チームが構成できるとよい。何よりも複合的な困難を持つ人を支えていくときに，1人の専門家の力ではすぐに壁にぶつかるので，チームの力が必要になってくる。そして精神科医にはそのチームをバックアップする役割が望まれる。吉田ら[11]は地域でのアウトリーチサービスの体制を整備するためには，地域の多機関が共同で協議する場，関係機関の役割分担や課題の明確化，ゲートキーパー役を作ることの重要性をあげている。現実には困難があるものの，地域の機関の中には医療機関も加わるべきであろうし，ゲートキーパー役は，本研究の結果からは，医療の側で担うべき部分が大きいと思われる。

本研究は都会にある一大学病院における調査であるので，どこまで一般化できるかについては検討を要する。特に新規外来患者についてはかなり医療機関の設置状況によって差異があると思われるため，生活支援が必要な人の割合については，さらなる調査が必要であろう。一方では外来患者の中に，診断分類を超えて，生活支援・ケアマネジメントが必要な人が一定程度存在することは事実であろう。こうした人を支援する体制を作るためには，それを可能にする医療経済体制だけではなく，生活支援と治療とを同時に行える多職種チームについての教育や研修を，医学教育の中に含めていく必要がある。

Slade[7]は，リカバリーを推進する精神保健システムの要件として，精神障害によって生じる特異的な問題への治療ではなく，むしろ日常的な生活の中で起こる日常的な支援が大切であると主張している。生活障害を持つ人が回復していくうえで，改めて生活支援の必要性を強調したものであるが，一方では疾病による脳機能をはじめとするさまざまな障碍と環境との複合的な連関を解き明かして，医療の役割を明確にしていく作業が伴わないと，なぜ地域での生活支援に医療機関が携わる必要があるかという根拠が見いだされないといえるだろう。生活における脳機能の役割や疾病の影響についての研究が求められていると考える。

さらに，よりよい精神保健福祉サービスにおいては，これまで縦割りであった医療と福祉とを統合していくことがより望ましいといえるだろう。そうしたことはどのようにして可能となるだろうか。

本研究は，厚生労働省科学研究費補助金 「地域生活中心」を推進する，地域精神科医療モデル作りと，その効果検証に関する研究（H23-実用化（精神）-指定-001）（主任研究者：伊藤順一郎）により実施された。

特に公表すべき利益相反はない。

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■第33回日本社会精神医学会（東京）：教育講演1

統合失調症の認知行動療法はどのようにして役立てることができるか—エビデンスと実際の適用

池淵恵美

抄録：
統合失調症の認知行動療法としては，1970年代よりSSTが体系化され，その後精神病症状を標的とする認知行動療法が広く行われるようになった。これまでの効果研究でSSTは社会的転帰を改善することと，精神病症状への介入で効果が得られることが，エビデンスとして確立してきている。しかし2008年のNICEガイドラインのためのレビューを皮切りに新しく出された複数のメタ解析では，コクランレビューも含め，陽性症状などに対して，他の精神療法と比べ優位性を確定できないか，小さい効果サイズしか期待できないとされている。統合失調症は生物学的基盤が大きく，一般的に心理社会的治療は大きな効果サイズを期待できない現状があると考えられる。しかしエビデンスを生み出す治験と実際の臨床との間にはそもそも乖離があることも踏まえて，SSTや精神症状に対する認知行動療法の持つ優れた点を臨床現場で生かすためには，薬物療法も含めた統合的な実施をしていく必要があること，均一のプロトコールに沿って平均値を求める治験と違う点として，個々のケースの価値観や好みや認識能力に合わせて，個別に実施することが有用性を高めるうえで重要であろう。治療者と患者との治療的協働作業のツールとして，認知行動療法は優れた方法論を持っており，地域ケアの時代には欠かすことのできない技術と考えられる。また地域の仲間集団の中で，認知行動的な技法がより生き生きと活用されている現状がある。

日社精医誌　23：188-195，2014

索引用語：統合失調症，認知行動療法，社会生活技能訓練（SST），心理社会的治療，エビデンスに基づく実践（EBP）

1．統合失調症の認知行動療法—歴史と概要

認知行動療法は，主に学習心理学に基づいて新たな適応的な行動の学習を促進する行動療法から発展して，行動だけではなく認知内容にも介入を行うものである。行動療法の学問的変遷の中で，1960年代から行動の学習における認知過程や自己コントロールの役割が重視されるようになった。外顕的行動だけではなく，主体である患者の内面が重視されるようになったのである。統合失調症に対しては1970年代よりSST（social skills training：社会生活技能訓練）が体系化され，そ

英文タイトル：How We Can Practice Cognitive Behavioral Therapy for Schizophrenia: Evidence and Clinical Adaptation
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れをもとに行動療法的家族援助(behavioral family management)が発展した。その後精神病症状を標的とする認知行動療法が広く行われるようになった。幻覚や妄想を対象とした認知行動療法は，精神病症状は薬物療法によって治療するもので，面接では中立的立場で関わるという精神医学の「常識」への挑戦といってよい。

統合失調症をはじめとする重度精神障害について，1970年前後から欧米諸国で脱施設化と地域ケアへの動きが広がってくる中で，それまでの病院内での治療やリハビリテーションから進んで，「社会の中で，当たり前に生活することを目標とする」ノーマライゼーションの理念が広がってきた。その中で，本人の強みを生かし，本人とともに，その希望に沿って生活できることを支援することや，自己選択権の重視などの治療理念と技術が発展してきた。そうした中で，認知行動療法の理論と技術は重要な役割を得ることになった。

統合失調症に対する認知行動療法の基本的な考え方は，Beckがうつ病の治療に用いた概念と技法を，統合失調症にも適用したものである。幻覚や妄想そのものは病的な体験であるが，同時に個別の状況から発生する個人的な体験であり，それに対する反応には個々人の意味づけや心理的健康を守る適応的な側面があるという治療的な仮説が基本にある。幻聴については，幻聴が聞こえる(A)→それに対する認知(B)→認知に伴う感情や行動(C)という，認知療法のABC図式を適用し，そのうえで認知をより適応的なものに修正する試みを行うというものである。

妄想についても幻聴と同様のABC図式が考えられている。認知はその人それぞれが持っている，世界を解釈する「ミニ理論」であって，その内容が結果的に本人にとって抑うつをもたらしたり不適応をもたらす場合に改変を試みる。Kingdonら[8]は，この「ミニ理論」は，一般的に流布される健康や精神障害についての誤った考え方や，民俗信仰的な考え方などと同様に，科学的根拠がないが多くの人が信じている「信念」に類似のものであり，訂正不能なものではないと考えている。もちろん幻覚や妄想が生じる基盤としては，認知機能障害が想定されるが，そうであっても病的体験の受け止め方については修正の余地があると，認知行動療法の理論家は考えるわけである。

2. これまでのエビデンス

1) 統合失調症の認知行動療法として初期に発達したSST

SSTはいくつかの認知行動的技法を組み込んだ学習パッケージで，社会的スキルの効果的な学習を目標としている。

Pfammatterら[14]は，統合失調症の心理社会的治療についてこれまでの無作為割り付けを行った研究報告をメタ分析しているが，SSTについては14研究を検討して，スキル獲得については0.77(CI 0.62-0.93)と中程度のエフェクトサイズが得られ，追跡調査では0.52であること，社会的機能の改善は0.39，精神症状の改善は0.23とエフェクトサイズが小さいことを報告している。Kurtzら[10]はSSTについての22研究をメタ分析し，対人スキルや日常生活のスキルの獲得についてはエフェクトサイズが0.57，地域生活機能0.52，陰性症状の改善0.40である一方，精神症状全般や再発防止についてはエフェクトサイズが小さいため，SSTの効果の及ぶ範囲について考察している。

2) 精神病症状への認知行動療法について規模の比較的大きな無作為統制研究が行われるようになった時代

統合失調症に対する認知行動療法の体系的レビュー[6]では，2004年までに印刷された19研究(30論文)について検討され，通常の治療と比較して，再発率や再入院率は減少しないが，入院期間は有意に減少すること，追跡調査で精神症状の改善が見られることなどが結論されている。このレビューで取り上げられた論文では，認知行動療法は急性期後の残存症状への心理的介入が中心であり，薬物療法抵抗性の症状の改善に有効[9]といった報告が含まれる。急性期での介入の報告では，

Druryら[1]は回復までの時間を短縮し，残存症状を減少させる効果があるとしている。

Tarrier[16]は20研究についてメタ分析を行い，慢性期の持続的な陽性症状を減少させる効果は明確だが，急性期の回復を促進する点については効果が小さく，早期介入についての効果はまだ明確になっていないとしている。Wykesら[18]の新たなメタ分析では，33研究を通して，標的症状の改善が0.40であることを示した。

Tandonら[15]は「統合失調症について明らかになっていること」と題した体系的なレビューの中で，明確な再現性・一貫性のある心理社会的治療の一つとして，「SSTは転帰を改善する」，「認知行動療法は精神病症状を減少させる」はある程度のエビデンスがあるとしている。

以上のように主に慢性期の陽性症状に対する有効性がこれまで報告されている。こうした研究を受け，統合失調症の転帰研究の専門チーム（the Schizophrenia Patient Outcomes Research Team[11]）は，推奨できる心理社会的治療の中に対人及び日常生活のスキルトレーニングと，薬物療法抵抗性の精神症状への認知行動療法を含めている。

3）新たなメタ解析の動向

2009年にNICEガイドラインの新たなレビュー[13]が発表されたが，統合失調症の認知行動療法の有用性についての結論は揺らがなかったものの，概括的症状の効果サイズは通常の治療と比較して−0.27（マイナスは認知行動療法のほうが対照治療に比べて有利であることを示す。他のactiveな治療法との比較では−0.13），同様に陽性症状に対しては−0.17（−0.13）と小さなものであった。

Hofmannら[3]はさまざまな精神障害に対する認知行動療法の効果についてこれまで実施された106件のメタ解析を検討し，最も頑健なエビデンスのあるものとして，不安障害，身体表現性障害，過食症，怒りと制御の障害，一般的なストレスへの効果を上げている。統合失調症に対しては，陽性症状や急性期の薬物療法を補完する治療としての有用性を示すメタ解析のほかに，再発防止や再入院防止にはほとんど効果がないとの解析が示され，頑健なエビデンスとまではいかないとしている。

最新のCochrane review[7]では精神病症状への認知行動療法についてのRCT 20件（31論文）を検討し，何らかの心理社会的治療と比較して，再発率，再入院率，陽性症状，陰性症状について有意差は見られなかったと報告している。社会機能については実施研究が少なく，認知行動療法の効果は明確ではなかった。実施研究数は少ないが，長期的な気分症状については効果がある可能性が指摘された。このメタ解析では認知行動療法と心理教育など，統合的な介入方法の治験については除外していることや，対照群として通常治療（Treatment As Usual）を設定した研究は除外し，対照として何らかのアクティブな心理社会的治療を行っている研究のみを取り上げるなど，厳しい選択基準をとっている。そのためにこれまで大きな効果が報告されている研究でも除外されたものがあることが，解析の結果に影響している可能性がある。そうした前提はあるが，このレビューの結論は「ほかの心理社会的治療と比べて，認知行動療法の明確な優位性は見られない」というものであった。

Jauharら[5]は，統合失調症に対する認知行動療法のメタ解析を行った。50研究が取り上げられ，概括的な症状に対する効果サイズ（−0.33，95% CI−0.4〜−0.19，マイナスは認知行動療法のほうが対照治療に比べて有利であることを示す），陽性症状（−0.25，95% CI−0.37〜−0.13），陰性症状（−0.13，95% CI−0.25〜−0.01）といずれも，「控えめな」効果サイズであった。Cochrane reviewと比べて対象研究は緩やかな選択基準であるが，結果に与えるバイアス（割り付け方，脱落率など）について検討したところ，評価者がブラインドで効果の査定を行っているかどうかが有意な影響を与えており，例えば陽性症状に対して，ブラインドである場合−0.08，ブラインドでない場合−0.57であった。2008年に新たにNICEの体系的レビューが発表されて以後，概括

的症状について評価したRCT 11研究のうち，有意な効果サイズが示されたのは2研究のみで，いずれもブラインドでの評価はなされていなかった。

以上のように近年のメタ解析では，統合失調症の認知行動療法の有効性については，明確ではないか，「小さい」効果サイズしか期待できないとする報告が主流となっている。これはなぜなのだろうか。

4）統合失調症に対する認知行動療法の効果をどう考えるべきか

まず統合失調症に対する一般的な心理社会的治療の持つ壁を考えたい。“just the facts”[15]という総説では，統合失調症についてほぼわかっていることを，疫学11項目，神経生物学（病態生理学）26項目，臨床所見24項目，治療及び予防16項目挙げているが，脳の構造や機能と関連した理解，例えば「全脳容積が減少し，両側の側脳室及び第3脳室が拡大している」「発症時より既に脳構造の異常が見られる」「ドーパミン作動薬は精神症状を悪化させ，D2拮抗薬は改善する」などが多く含まれている。統合失調症の病態は，広く神経病理・生理・薬理学的なアプローチでの究明が行われており，そのためにこの総説で取り上げられている治療も，16項目のうち9項目は薬物療法に関するものである。生物学的な治療基盤のもとで，心理社会的治療は適用されており，一般的に効果研究で得られる効果サイズは必ずしも大きいものではないことは，前提として考える必要がある。

新しい治療法の開発とその後の検証の過程をみると，少なくとも統合失調症の心理社会的治療については，検証方法が厳密になり，治療法の新奇性や人々の期待が薄れるにつれ，例外はあるにしろ報告される効果サイズは小さなものになるように，筆者には感じられる。それは抜本的な心理社会的「治療」がまだ開発されていないということの証左であろうか。

しかしながら，SSTや精神症状に対する認知行動療法が，一般的な介入に比べて，標的目標に対し一定の効果を上げていることは否定できない事実である。私たち専門家は，目の前にいる困難を抱えた患者さんたちに対し，可能な限りの知識や技術で，最善の治療をする義務がある。それでは統合失調症の認知行動療法はどのように活用できるだろうか。それを考える前に，エビデンスという方法論の持つ利便性と限界についてまずはふれたい。

3. エビデンスとは？

1）エビデンスの利便性と限界

エビデンスが示されていない治療法はそもそも，実際に患者さんに提供する根拠に乏しいことは明らかであろう。そしてエビデンスを参照することにより，平均的な集団を対象として，どの程度確実に，どのような効果が得られるかを予測することができる。見立てや治療計画や説明と同意に当たり，エビデンスは欠かすことができない。

一方で，個別の患者さんを目の前にして，どのような治療を行おうかと考える時に，治療ガイドラインを参照しようとすると，大まかな枠組みしかガイドラインでは示してくれないので，失望した経験をお持ちの方も多いのではないだろうか。治療ガイドラインは，「誰に」「いつ」「どのように」適用するかについての情報に乏しい。これは平均値を求めるエビデンスの方法論によるところが大きい。Aさんには+1.2の効果があり，Bさんには効果がゼロであるが，平均としては+0.6の効果という数値が出てくるわけである。

2）エビデンスを創出するための無作為割り付け統制研究と一般臨床とは乖離がある

効果を実証するためには，介入変数を決め，その他の条件は統制し，媒介変数を絞り込んで，介入変数の効果が明確になるように治験をデザインする。認知行動療法という治療以外の条件は同一にして，認知行動療法のみの効果量を知ろうとするわけである。これは還元主義の考え方である。一方で臨床の現場では，さまざまな治療によいと考えられる変数を組み込んで，お互いの相互作用

を考えつつ優先順位をつけて実施するといった，統合主義の考え方がとられる。認知行動療法のみ行うわけではなく，むしろいろいろな治療法の相乗的な効果を期待する。一つ一つの治療法は独立しては力が弱いといってもよい。またConsort声明などで掲げられている，評価の盲検化，無作為割り付け，厳密な除外基準など，質の高い治験を行うための制約は，明らかに臨床での営みから離れる人工的な制約である。

また治験の場合には，一般的に数量化できる客観的指標を用いる。主観的な治療者の印象「どこか手ごたえを感じる」や，患者さんの感想「とても元気になってきました」についてはほとんど用いられない。しかしそれによって，特に精神科領域では大切な治療についての情報がかなり失われてしまうように感じられる。面接で得られる豊富な情報を，どの程度数量化した客観指標に集約することができるだろうか。近年ではがん治療など身体治療の領域でも，Patients-Reported Outcomeといわれる，当事者の側の主観的評価を重視する動きがあり，より臨床現場での体験を反映しようとしている。しかしまだ今のところ，治験における主要アウトカムとしてこうした指標を取り上げるものはほとんどないといってよいだろう。

3）エビデンスに基づく治療は実際どの程度普及しているか

これまで述べてきた精密で人工的な治験と臨床現場との乖離という，エビデンスにまつわる本質的な問題と，質の高い医療をなかなか提供できない現実的な制約の双方から，エビデンスのある治療が標準治療として十分普及していないという現実がある。

英国では早くから，重度精神障害についても病院医療から地域ケアへの転換が行われており，一方で統合失調症の認知療法研究についても優れた研究者が多数存在するが，地域ケアで必ずしも体系的な認知行動療法は実施されていない。NICEガイドラインで推奨されているにもかかわらず，である。

実践的な短期認知療法の効果研究として，Turkingtonら[17]の報告がある。治療に携わる地域ケア看護師にあらかじめ10日間のトレーニングが実施され，422名の統合失調症と診断され地域で生活する人が，無作為に認知療法群(3ヶ月間に6回の個人認知療法で，パンフレットを用いた心理教育も含む，希望のある家族などの援助者に3回までの同様のセッション)と対照群(通常の地域ケア)に，2：1の割合で割り付けられた。認知療法群の方が有意に概括的症状，病識，抑うつが改善していた。このように，普及モデルの開発，すなわち精神科臨床サービスの提供研究を行うことも，先に述べた矛盾を解消していくために必要があるだろう。

4. 臨床の現場でどのように活用することができるか

1）統合失調症に対する心理社会的治療を臨床で活用するための前提

すでに述べてきたようにエビデンスがなければ，治療を行う根拠がない。しかしエビデンスを生み出す無作為割り付け統制研究は，臨床現場での営みとの乖離がある。しかも統合失調症の認知行動療法では，小さな効果サイズしか今のところ保証されていない。そうした中で，実際に認知行動療法が患者さんの役に立つためのカギを握るのは，統合的な実施ということと，個別の治療計画によって実施していくということである。

統合的な実施についてはすでにふれているが，統合失調症の心理社会的介入はいずれもそれぞれ標的があり，しかもそれ以外の領域への波及効果は小さい事情があり，患者さんのニーズに広く答えていくためにはさまざまな心理社会的介入を必要に応じて，しかも統合的に使っていくことが必須である。薬物療法は陽性症状の改善や再発防止効果が明確であるが，陰性症状や社会的機能の改善については十分な力を発揮しないところからも，薬物療法単独の治療は，よい医療とは言えない。心理社会的治療についても事情は一緒である。

個別化ということは，治験ではプロトコールに沿って均一な介入プログラムが求められることとは対照的に，個々のケースの評価に沿ってカスタマイズして実施し，本人の志向や価値観を重視するということである。自身の症状に関心を持ち，変えようと思う人もいれば，そうしたことには価値を見出さず，スポーツ療法などを好む人がいる。関心と意欲がなければ，本人が力を発揮し，自分の生活の中で生かしていけることは生まれない。そこが個別化の必要性が生じるところであり，平均値を求める治験との違いである。

2) 個別の希望や目標に沿って活用する必要がある。

認知行動療法について，効果の般化が課題となることがしばしばある。なぜ「般化」が難しいのだろうか。幻聴への注意焦点付けやオペラント条件付けなどの技術は，介入に時間がかかる一方，介入の中止によって効果が失われる（または病院内では実行できても日常生活での般化が困難）との報告があり，自己対処として十分学習されない可能性があった。Haddockら[2]は幻覚や妄想に対する認知行動療法の総説の中で，いろいろな状況で患者自らが使おうとすることや，体験症状をコントロールするための手がかりを日常生活の中に見つけていくことが般化につながることを指摘している。つまり自分で使ってみて，自分のものにしていく過程が必須であるということである。ここでも前述の本人の希望や志向を踏まえつつ，一緒に目標を作っていくプロセスが必要になる。

統合失調症に限らず，認知行動療法に共通の技術として，日記などを用いたセルフモニター，精神症状の医学的成因についての情報提供，症状のもたらす認知-行動-感情の関係を共有する，対処方法を探しその習得を援助する，などがあるが，これらはいずれも治療者と患者との治療的共同作業のツールとなる。統合失調症の人が，地域で当たり前に生活できることを支援しようとする考え方の中で，こうした技術やツールは極めて有用である。例えば薬物療法を継続することは，再発防止率を高める最も有効な手段であるが，服薬中断による再燃や再入院が長らく大きな問題であった。そして「統合失調症の人は病識が欠如している」という理解がかつては主流であった。病識欠如[4]が治療を妨げる深刻な障壁であることは今も変わらないが，その障壁の克服のために，薬物療法について，本人にもわかりやすく情報を提供し，服薬行動についての学習を促進し，薬物の効果についてのセルフモニターや副作用についての対処法を促し，また専門家と連携するコミュニケーション技術の学習を援助することが行われるようになってきた。こうした考え方や技術の発展に，認知行動療法は大きく貢献している。

統合失調症のもたらす障害を認識し，対処していく力を育むうえでは，仲間集団の貢献も大きい。向谷地[12]は浦河べてるの家の経験から，「統合失調症の体験も恥じることなく語る文化の中で，見えてきた当事者の抱える『本質的な生きづらさ』が，単なる社会サービスの充実や病気の回復を越えた実存的な課題として浮上してきた。それはアルコール依存症者が『酒だけやめても何の解決にもならない』という言葉に似ている」と述べている。こうした仲間集団の中で，認知行動的な技法がより生き生きと活用されることが見られるようになっている。

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abstract

How We Can Practice Cognitive Behavioral Therapy for Schizophrenia : Evidence and Clinical Adaptation

Emi Ikebuchi

As cognitive behavioral therapy for schizophrenia, social skills training (SST) had developed since early 1970, and Cognitive behavioral therapy (CBT) targeted at psychotic symptoms has followed and disseminated. Intervention studies have verified until recently that SST improved social functioning and CBT decreased psychotic symptoms. However several meta-analysis (Cochrane systematic review and so on) have published since 2008, and reported that CBT had no significant effect over other psycho-social treatment, or small effectsize as compared with control therapy. Schizophrenia bases broadly biological etiology, so psychosocial treatment as general have not so large impact. There is a discrepancy between intervention studies and real world practice : unified protocol for diverse subjects, no use of combined psychosocial treatments, only objective outcome variables, and so on. In real world practice we can use SST and CBT effectively under condition of combined pharmacotherapy and several psychosocial treatments and individualized treatment plan considering patient's values and preferences. CBT is thought to be very useful as a tool for collaborating with patients in community based treatment. CBT is also observed its effectiveness in peer support group.

Key words : *schizophrenia, cognitive behavior therapy, social skills training (SST), psycho-social treatment, evidence based practice (EBP)*

Jpn Bull Soc Psychiat 23:188-195, 2014

Department of Psychiatry, Teikyo University School of Medicine

Psychiatry Research 226 (2015) 494–498

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Relationship between hypothalamic–pituitary–adrenal axis dysregulation and insulin resistance in elderly patients with depression

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ARTICLE INFO

Article history:
Received 23 July 2014
Received in revised form
9 January 2015
Accepted 19 January 2015
Available online 24 February 2015

Keywords:
Depression
Insulin resistance
Homeostasis model assessment of insulin resistance (HOMA-R)
Hypothalamic–Pituitary–Adrenal (HPA) axis
Diabetes
Dexamethasone (DEX/CRH) test

ABSTRACT

Cortisol dysregulation has been proposed to be involved in depression. Hypothalamic–pituitary–adrenal (HPA) axis dysregulation associated with major depressive disorder (MDD) was previously reported to be higher in the elderly. Furthermore, insulin resistance and the prevalence of type 2 diabetes are known to increase with aging. The aim of the present study was to determine whether a relationship existed between plasma cortisol levels following the dexamethasone/corticotrophin-releasing hormone (DEX/CRH) test and insulin resistance evaluated by the homeostasis model assessment of insulin resistance (HOMA-R) in elderly MDD subjects. Fifteen unmedicated MDD inpatients and 17 age- and sex-matched healthy controls participated in this study. After overnight fasting, blood samples were collected to measure plasma glucose and insulin concentrations, estimate HOMA-R, and perform the DEX/CRH test to evaluate HPA axis function. The value of the area under the time curve of plasma cortisol concentrations ($Cort_{AUC}$) and peak cortisol values ($Cort_{peak}$) following the administration of DEX/CRH both correlated with HOMA-R in MDD group. In contrast, neither $Cort_{AUC}$ nor $Cort_{peak}$ correlated with HOMA-R in controls. This is the first study to directly demonstrate the relationship between HPA axis dysregulation assessed with the DEX/CRH test and the index of insulin resistance estimated as HOMA-R in elderly MDD patients.

1. Introduction

A relationship has been identified between MDD and type 2 diabetes, which have also been proposed to partially share a common etiology (Iwata et al., 2013); MDD was shown to increase the incidence of type 2 diabetes (relative hazard [RH] 1.63, 95% CI 1.31–2.02) (Golden et al., 2004) and the comorbidity rate of MDD in type 2 diabetic patients was estimated to be higher than that in the non-diabetic population (Gavard et al., 1993). A meta-analysis performed by Gavard et al. (1993) revealed that the prevalence of depression in current diabetic patients ranged between 8.5% and 27.3% (mean=14.0%), which was three-fold higher than the prevalence of MDD in the general adult population.

The risk factors for MDD in diabetic patients include the burden of diabetes management and arteriosclerosis (Schillerstrom et al., 2008). On the other hand, the risk factors for diabetes in patients with depression involve reduced daily activities, overeating, and hypercortisolemia (Pariante and Lightman, 2008). Hypercortisolemia has been attributed to hypothalamic–pituitary–adrenal (HPA) axis dysregulation, which is one of the most reliable biological findings of MDD (Pariante and Lightman, 2008), has been implicated in the development of insulin resistance (Manoudi et al., 2012), and is a risk factor for type 2 diabetes (Brown et al., 2004). However, evidence for the relationship between hypercortisolemia and insulin resistance is limited to a cross-sectional study that only recruited normal volunteers (Rizza et al., 1982). This study demonstrated that cortisol-induced insulin resistance was caused by a decrease in both hepatic and extrahepatic sensitivity to insulin.

HPA axis dysregulation associated with MDD was previously shown to be more prevalent in the elderly (Hatzinger et al., 2011), and insulin resistance and the prevalence of type 2 diabetes have both been reported to increase with aging (Rowe et al., 1983). Regarding depression, community-based studies identified a relationship between aging

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http://dx.doi.org/10.1016/j.psychres.2015.01.026

and prevalence of MDD (Beekman et al., 1999; Naismith et al., 2012). Moreover, a meta-analysis revealed that aging itself may be an important risk factor for MDD (Snowdon, 2001). A previous study also found that the prevalence of type 2 diabetes was the highest in the elderly (Danaei et al., 2011). Taken together, these findings suggested that a positive relationship exists between hypercortisolemia arising from HPA axis dysregulation and insulin resistance in elderly MDD patients.

Elevated cortisol levels have been shown to worsen glucose tolerance (Di Dalmazi et al., 2012). Insulin resistance may aggravate type 2 diabetes and cardiovascular disease, but not hypercortisolemia, which may develop due to the excess secretion of adrenocorticotrophic hormone (ACTH) or administration of a glucocorticoid treatment, but not directly from insulin resistance (Meigs, 2003; Prague et al., 2013). Therefore, we hypothesized that depression or depressive episodes may have effects on cortisol dysregulation and also that the resultant hypercortisolemia may subsequently lead to the development of insulin resistance in patients with depression. In the present study, we investigated whether hypercortisolemia resulting from HPA axis dysregulation was directly associated with insulin resistance in elderly MDD patients. The primary aim of the present study was to determine whether plasma cortisol levels following the dexamethasone/corticotrophin-releasing hormone (DEX/CRH) test correlated with insulin resistance evaluated with HOMA-R in elderly MDD subjects.

2. Methods

2.1. Subjects

Fifteen unmedicated inpatients from the psychiatry ward, Tottori University Hospital, Yonago, Japan and 17 age- and sex-matched controls participated in this study with written informed consent between November 2008 and December 2012 following a full explanation of the study. All were older than 60 years. Fifteen inpatients met the criteria of MDD from the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV). The diagnosis of MDD was then confirmed by Mini-International Neuropsychiatric Interview Control (M.I.N.I) (Sheehan et al., 1998). Seventeen control subjects were recruited from the community in Tottori, Japan via an official employment agency. They met neither current nor lifetime axis I disorders of DSM-IV, which was then confirmed by M.I.N.I. Exclusion criteria for all subjects were as follows; (1) somatic disorders such as diabetes, chronic inflammatory disease, autoimmune disease, endocrine disease, and neoplasm, which directly or the treatment of which could influence insulin resistance or plasma cortisol levels; (2) clinical evidence of other central nervous system disorders based on a clinical history and medical examination. Mental ability was examined using the Mini-Mental State Examination (Folstein et al., 1975) with a cut-off point of 24; (3) a current or past history of the abuse of illegal drugs or other substances such as benzodiazepines and alcohol; (4) past history of a head injury; and (5) taking any psychotropic drug such as antipsychotics, antidepressants, and mood stabilizers for the preceding two weeks prior to this study because these drugs are known to influence the HPA axis and insulin resistance (Bergman and Ader, 2005; Bschor et al., 2011; Kunzel et al., 2003; Mondelli et al., 2010).

This study was approved by the Ethics Committee of Tottori University Faculty of Medicine and all subjects gave written informed consent after a full explanation of the study.

2.2. Physical measurements and depression scale assessment

The heights (m) and weights (kg) of elderly MDD subjects were measured on admission, and just before this study for the control subjects. The Hamilton depression scale (HAM-D17) (Hamilton, 1960) was assessed in elderly MDD subjects.

2.3. Assessment of HPA function

The DEX/CRH test is the most sensitive measurement of HPA axis regulation (Kunugi et al., 2012), and was, thus, conducted to assess HPA axis regulation in all subjects. The test was performed with a PO pretreatment of 1.5 mg DEX ('decadron' 0.5 mg, Nichiiko Pharmaceutical Corporation, Toyama, Japan) at 23:00 h. An IV catheter with heparinized physiological saline was inserted into a forearm vein at 14:30 h on the following day, and 100 μg human CRH (hCRH 'TANABE', Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) was injected through the catheter at 15:00 h immediately after the first (= 0 min) blood sampling. Blood samples were taken 30, 60, and 90 min after the injection of CRH in order to measure plasma ACTH and cortisol concentrations. Subjects rested supine in hospital beds throughout the test. Blood samples were cooled in ice water, rapidly centrifuged in a tube for 10 min at 3000 rpm at 4 °C, and then stored at −20 °C until later analyses. Plasma ACTH and cortisol concentrations were measured using an electrochemiluminescent immunoassay and chemiluminescent enzyme immunoassay, respectively, at SRL Co. (Tokyo, Japan). The limits of detection for ACTH and cortisol were 5.0 pg/ml and 1.0 μg/dl, respectively. $ACTH_{base}$ and $Cort_{base}$ were defined as the plasma concentrations of ACTH and cortisol, respectively, in the blood sample obtained at 15:00 h. $ACTH_{30}$, $ACTH_{60}$, and $ACTH_{90}$ were defined as the plasma ACTH concentrations measured 30, 60, and 90 min, respectively, after the IV infusion of CRH. $Cort_{30}$, $Cort_{60}$, and $Cort_{90}$ were similarly designated for plasma cortisol concentrations. The area under the time curve (AUC) was calculated according to the trapezoidal rule (e.g. $Cort_{AUC}$ for the AUC of cortisol). $Cort_{peak}$ was the peak value of the plasma cortisol concentration in response to CRH. $ACTH_{AUC}$ and $ACTH_{peak}$ were defined in a similar manner. Regarding criteria for the suppression of cortisol levels with DEX, we followed those described in a previous study (Kunugi et al., 2012), in which abnormal "non-suppression" was defined as $Cort_{base}$ of ≥ 5.0 μg/dl irrespective of the size of $Cort_{peak}$, and "intermediate-suppression" as $Cort_{base}$ of < 5.0 μg/dl and $Cort_{peak}$ of ≥ 5.0 μg/dl.

2.4. Assessment of insulin resistance

In the present study, insulin resistance was assessed with the homeostasis model assessment of insulin resistance (HOMA-R) because it is one of the most extensively used measurements of insulin resistance in clinical settings (Wallace et al., 2004). Its formula is the basal insulin level multiplied by the basal plasma glucose concentration divided by 22.5. Normal values were previously estimated as 1.62 ± 0.96 (Matthews et al., 1985). After overnight fasting, blood samples were collected to determine plasma glucose and insulin concentrations. Plasma glucose levels were measured using an enzymatic assay and plasma insulin levels were measured using a chemiluminescent immune assay at SRL Co.

2.5. Schedule of the hormonal examination

Blood samples were collected on the first day. The PO pretreatment with 1.5 mg DEX was conducted on the second day at 23:00 h, and the DEX/CRH test was conducted on the third day.

2.6. Statistical analysis

In order to make comparisons between patient and control groups, an unpaired *t*-test was used to assess differences in the following items; age, BMI, and fasting blood sugar (FBS). The Mann–Whitney test was used to assess differences in the following items; $Cort_{peak}$, $ACTH_{peak}$, $Cort_{AUC}$, $ACTH_{AUC}$, and HOMA-R. Fisher's exact test was used to assess differences in the ratio of sex, non-suppression, and intermediate-suppression between the two groups. Spearman rank correlation coefficients were determined to assess the relationships among age, BMI, HAMD, and hormonal parameters, such as ACTH, cortisol, and HOMA-R because of the strongly skewed distribution of these hormonal parameters. A value of $p < 0.05$ was considered significant. Data analyses were performed using SSPS for Windows 17.0 (SSPA Inc. Chicago).

3. Results

The demographic and clinical characteristics of the elderly MDD patients and control subjects are shown in Table 1. No significant differences were observed in these characteristics or FBS, $Cort_{peak}$, $Cort_{AUC}$, $ACTH_{peak}$, $ACTH_{AUC}$, and HOMA-R between the two groups (Table 2). The ratio of the number of participants assessed as abnormal, non-, and intermediate-suppression in the DEX/CRH test was significantly higher in the patient group than in the control group (Fisher's exact test; $p < 0.05$, φ coefficient 0.39) (Table 3).

Metabolic characteristics, endocrinal responses, age, and HAMD for the elderly MDD subjects, controls, and all subjects are shown in Table 4. No correlation was observed between BMI and endocrinal parameters in all subjects, in the control subjects, and in the elderly MDD patients, with the exception of a correlation between BMI and HOMA-R in all subjects (Rho=0.48; $p < 0.05$) and in the control subjects (Rho=0.76; $p < 0.05$). However, this correlation was not found in the elderly MDD patients. Regarding the relationship

between HPA axis function and insulin resistance, indices of the HPA-axis, $Cort_{peak}$ and $Cort_{AUC}$ did not correlate with HOMA-R in all subjects and in the control subjects. However, $Cort_{AUC}$ and $Cort_{peak}$ both correlated with HOMA-R in the elderly MDD patients (Rho= 0.56; $p<0.05$, Rho=0.54; $p<0.05$, respectively). The relationships between $Cort_{AUC}$, $Cort_{peak}$, and HOMA-R in all subjects, the control subjects, and the elderly MDD patients are shown in Fig. 1. In the elderly MDD patients, the total HAMD score correlated with $Cort_{peak}$ (Rho=0.80; $p<0.05$) and $Cort_{AUC}$ (Rho=0.83; $p<0.05$), as shown in Fig. 2. The total HAM-D score did not correlate with HOMA-R. Furthermore, no correlation was observed between age and either BMI or endocrinal parameters.

4. Discussion

In the present study, correlations were observed between $Cort_{AUC}$ or $Cort_{peak}$ obtained from the DEX/CRH test and HOMA-R, an index of insulin resistance, in the elderly MDD patients. This is the first study to directly demonstrate the relationship between HPA axis dysregulation, as revealed by the DEX/CRH test, and insulin resistance in elderly MDD patients.

The correlation between cortisol dysregulation and insulin resistance was only observed in the elderly MDD patients. Additionally, the ratio of participants showing abnormal, non-, or intermediate-suppression of the DEX/CRH test was higher in the elderly MDD patients. Thus, although this study had a cross-sectional design in nature and, thus, cannot concretely conclude any relationship between elevated cortisol levels and insulin resistance, our results are consistent with the hypothesis that depressive states affect cortisol dysregulation, and also that hypercortisolemia leads to the development of insulin resistance in elderly patients with depression.

A correlation was observed between BMI and HOMA-R in the control subjects, but not in the MDD patients. A previous study reported that obesity was associated with an increased risk of developing insulin resistance. In obese individuals, adipose tissue releases increased amounts of non-esterified fatty acids, glycerol, hormones, pro-inflammatory cytokines, and other factors that are involved in the development of insulin resistance. The lack of a significant relationship between obesity and insulin resistance in elderly MDD patients may be explained by the relatively larger effect of elevated cortisol levels on insulin resistance in this population.

To examine the relationship between cortisol and HOMA-R, a multivariate analysis was considered to be appropriate in order to assess the contribution of BMI and age; previous studies demonstrated that BMI was positively associated with insulin resistance (Mihic and Modi, 2008; Tjokroprawiro, 2006), and a weak negative association has also been reported between BMI and plasma cortisol levels (Travison et al., 2007). On the other hand, the HPA axis associated with MDD was reported to be more prevalent in the elderly (Hatzinger et al., 2011), and insulin resistance and the prevalence of type 2 diabetes have both been shown to increase with aging (Rowe et al., 1983), as discussed above. However, no

Table 1
Demographic and clinical characteristics of the patient and control groups.

	MDD	Control	*p*-value
	($n=15$)	($n=17$)	
Age (yr), mean (SD)	71.5 (7.0)	70.2 (6.0)	n.s [a]
Male/Female	7/8	7/10	n.s [b]
BMI (kg/m^2), mean (SD)	20.7 (3.3)	22.1 (3.1)	n.s [a]
HAMD	22.7 (7.8)		

[a] Unpaired *t*-test.
[b] Fisher's exact test.

Table 2
Hormonal parameters in elderly MDD patients and control subjects.

	MDD	Control	*p*-value
FBS	98.9 (20.5)	98.58 (12.65)	n.s[a]
HOMA-R	1.26 (0.66)	1.01 (0.81)	n.s[b]
$Cort_{peak}$	9.4 (9.8)	2.73 (2.56)	n.s[b]
$Cort_{AUC}$	663.6 (705.7)	181.5 (134.0)	n.s[b]
$ACTH_{peak}$	33.3 (38.4)	9.27 (12.1)	n.s[b]
$ACTH_{AUC}$	2156.6 (2465.0)	604.68 (699.2)	n.s[b]

[a] Unpaired *t*-test.
[b] Mann–Whitney test.

Table 4
Metabolic characteristics, endocrinal responses, age and HAMD for the elderly MDD subjects,controls, and all the subjects.

MDD $n=15$				
	BMI	HOMA-R	Age	HAMD
HOMA-R	0.35	–	0.99	0.37
$Cort_{peak}$	−0.92	0.54*	0.85	0.80*
$Cort_{AUC}$	−0.13	0.56*	0.93	0.83*
$ACTH_{peak}$	−0.08	0.30	0.86	0.68*
$ACTH_{AUC}$	−0.08	0.35	0.88	0.66*
Age			–	
HAMD	−0.18	0.37	0.93	–
Controls $n=17$				
HOMA-R	0.76*	–	0.93	
$Cort_{peak}$	−0.18	−0.06	0.52	
$Cort_{AUC}$	−0.89	−0.11	0.43	
$ACTH_{peak}$	0.25	−0.19	0.51	
$ACTH_{AUC}$	−0.12	−0.19	0.40	
Age			-	
MDD+controls $n=32$				
HOMA-R	0.48*	–	0.60	
$Cort_{peak}$	−0.07	0.23	0.47	
$Cort_{AUC}$	−0.12	0.23	0.38	
$ACTH_{peak}$	−0.16	0.07	0.99	
$ACTH_{AUC}$	−0.17	0.09	0.84	
Age			–	

Spearman's Rho.
* $P<0.05$.

Table 3
Ratios of abnormal non-suppression and intermediate suppression in the elderly MDD patients and control subjects.

	MDD	Control	φ coefficient	
Non-suppression[a]	7/15(46.7)	2/17(11.8)	$p<0.05$	0.39
Intermediate suppression[b]	0/15(0.0)	0/17(0.0)		
Non-suppression and intermediate suppression	7/15(46.7)	2/17(11.8)	$p<0.05$	0.39

φ coefficient Fisher's exact test.
[a] Defined as $Cort_{base}$ of ≥ 5.0 μg/dl irrespective of $Cort_{peak}$.
[b] Defined as $Cort_{base}$ of <5.0 μg/dl, $Cort_{peak}$ ≥ 5.0 μg/dl.

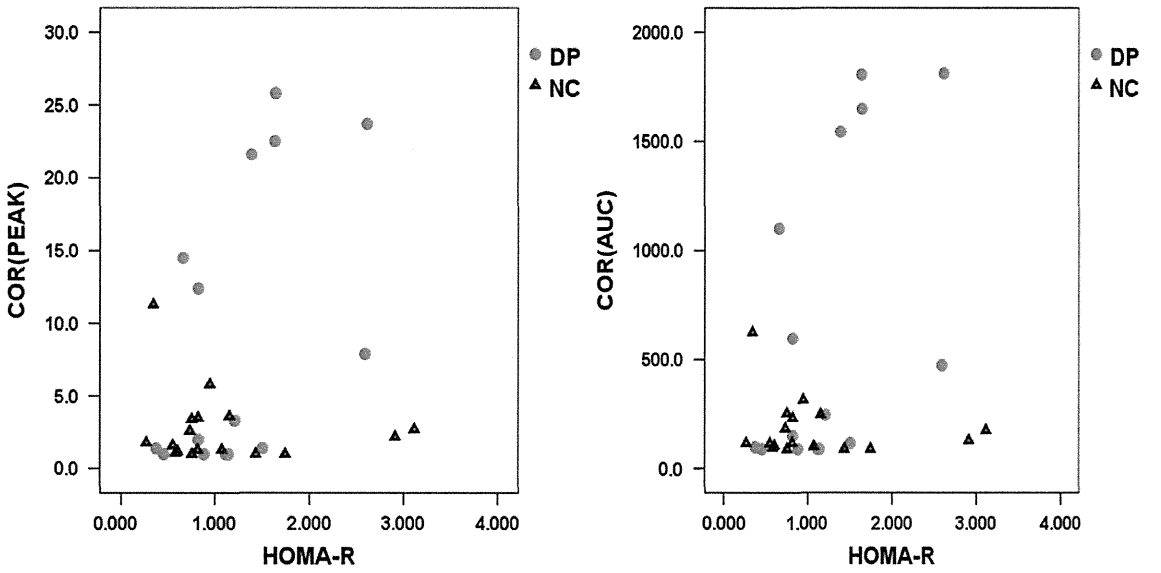

Fig. 1. Shows the correlation between $Cort_{peak}$ and $Cort_{AUC}$ and the DEX/CRH and HOMA-R of all the subjects, the control subjects, and the elderly MDD subjects. $Cort_{AUC}$ and $Cort_{peak}$ both correlated with HOMA-R only in the elderly MDD subjects (Rho=0.56; $p < 0.05$, Rho=0.54; $p < 0.05$, respectively).

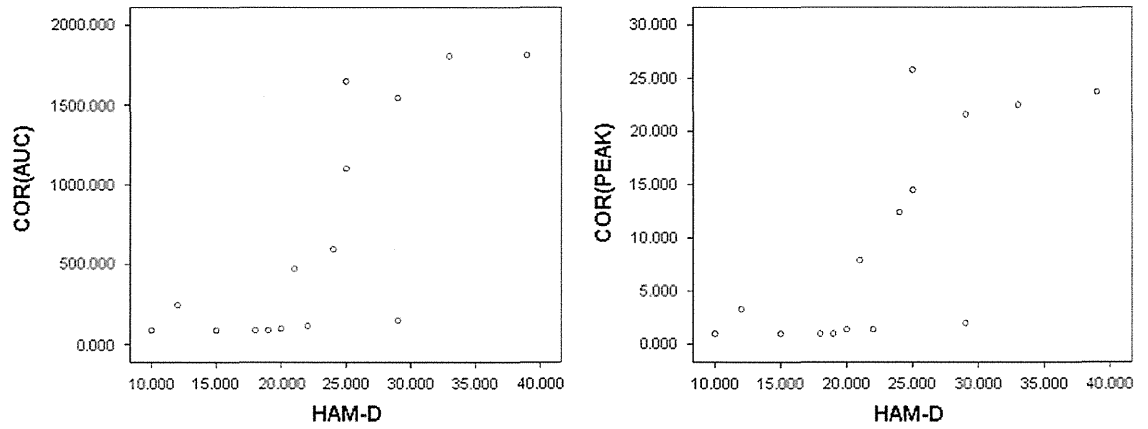

Fig. 2. HAMD correlated with $Cort_{peak}$ (Rho=0.80; $p < 0.05$) and $Cort_{AUC}$ (Rho=0.83; $p < 0.05$) in the elderly MDD subjects.

correlation was observed between BMI and plasma cortisol levels or HOMA-R nor between age and plasma cortisol levels or HOMA-R, in the elderly MDD patients in the present study; therefore, we adopted a univariate analysis.

Our results also indicated that the severity of the psychiatric condition positively correlated with plasma cortisol levels. Recent studies demonstrated that patients with more severe depression had higher cortisol levels (Kunugi et al., 2006; Owashi et al., 2008), and our results were consistent with these findings. On the other hand, we did not find any correlation between the severity of the psychiatric condition and the index of insulin resistance assessed with HOMA-R. Therefore, we hypothesized that a depressive state may affect cortisol dysregulation, and that hypercortisolemia may then worsen insulin resistance in elderly patients with depression.

In the present study, no significant differences were observed in any hormonal parameter such as $Cort_{peak}$ and $Cort_{AUC}$ between control subjects and the elderly MDD patients (Table 2). Although previous studies reported significant differences in these parameters between these groups (Kunugi et al., 2004), others disproved such differences in HPA regulation between healthy controls and depressed subjects (Carpenter et al., 2009; Gervasoni et al., 2004). HPA axis dysregulation was not detected in patients with the following attributes: being outpatients, chronic patients, long-term sick leave patients, and atypical depression patients (Kunugi et al., 2012), who were not investigated in our study. Since the ratio of abnormal, non-, and intermediate-suppression was significantly higher in the patient group, the weak statistical power due to the small number of subjects may be the reason for the apparent lack of significant differences in hormonal parameters between the two groups.

The number of adults over 60 years old is increasing in many developed countries (Christensen et al., 2009). Although previous studies demonstrated that depression indirectly influenced the physical health of the elderly through cognitive impairments and social factors such as a lower income and poor social support (Mezuk et al., 2012; Takeshita et al., 2002), depression, per se, may directly affect the physical health of the elderly through insulin resistance and type 2 diabetes. From a clinical perspective, clinicians should consider the risk of type 2 diabetes when they treat elderly MDD patients.

The limitations of the present study are as follows: (1) the small sample size; the number of participants in this study was relatively small. The responses of the HPA axis, such as cortisol responses, were highly variable ($Cort_{peak}$; mean 5.8, S.D. 7.6, $Cort_{AUC}$; mean 407.5, S.D. 542, for all subjects); thus, a large sample size is more desirable. (2) The cross-sectional design; a longitudinal study is required to establish a relationship between depression, HPA dysregulation, and insulin resistance. (3) The limited characteristics of the subjects; only inpatients and the

elderly were included in this study. Outpatients, remitted patients, and other generations of subjects are needed to more accurately examine the relationship between HPA dysregulation, insulin resistance, and age; however, it is possible that the correlation observed between cortisol levels and insulin resistance may be specific to elderly patients. (4) Other limitations include the lack of consideration of the duration of the current depressive episode, frequency of depressive episodes in the life of the patient, the nature of the depressive state, such as psychotic or non-psychotic, typical or atypical, and a family history of diabetes. (5) The multiplicity of the statistical tests was not considered, and, thus, in combination with the small sample size, the results of the present study should be taken as exploratory at best.

Role of the funding sources

We received research funding from Tottori University Hospital.

Conflict of interest

We declare that we have no conflicts of interest.

Acknowledgments

We thank Youichi Kurozawa for his assistance with data management. We are also thankful to the medical staff at Tottori University for their assistance with this study.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.psychres.2015.01.026.

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Journal of Psychiatric Research 62 (2015) 62–70

Contents lists available at ScienceDirect

Journal of Psychiatric Research

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Prefrontal activation predicts social functioning improvement after initial treatment in late-onset depression

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ARTICLE INFO

Article history:
Received 16 July 2014
Received in revised form
15 January 2015
Accepted 16 January 2015

Keywords:
Late-onset depression
Near-infrared spectroscopy
Social Adaptation Self-Evaluation Scale
Prefrontal cortex

ABSTRACT

The activation of oxygenated hemoglobin (oxy-Hb) has been shown to be lacking in the prefrontal cortex (PFC) of patients with late-onset depression (LOD), in verbal fluency task (VFT)-related near-infrared spectroscopy (NIRS). In our previous studies, we have emphasized the connection between the lack of activation in the frontopolar cortex and social functioning disorder in patients with LOD. In this study, we investigated whether the responsiveness to medical treatment of untreated patients with LOD, particularly social functioning improvements, could be predicted by NIRS findings at the initial examination. The subjects were 29 patients with LOD who were diagnosed with major depression at 65 years or older at the initial examination (mean age ± standard deviation, 72.4 ± 5.71 years). We measured the changes in hemoglobin concentration in the prefrontal and temporal cortex regions during a VFT by using 52-channel NIRS. In addition, depression status and social functioning were evaluated with the Hamilton Depression Rating Scale and the Social Adaptation Self-evaluation Scale, respectively, at the initial examination and 8 weeks after the treatment. A negative correlation was found between the NIRS activation in the right ventrolateral PFC region before treatment and the improvement in social functioning. These results suggested that the social functioning improvements were greater in LOD with initially lower NIRS activation in the right ventrolateral PFC region. NIRS is a simple technique that can be used before treatment to evaluate the social functioning levels of patients with LOD, and predict social functioning improvement after treatment.

1. Introduction

As the aging of populations continues in society, there has been a growing interest in psychiatric disorders in the elderly (WHO, 2008). Depression, which is a disease with a high prevalence, is common in the elderly in the general population (Blazer, 1989; NIH consensus conference 1992). In recent years, increased knowledge of the disease and the increased use of pharmacotherapy with new-generation antidepressants such as selective serotonin reuptake inhibitors and selective serotonin noradrenaline reuptake inhibitors have resulted in improved treatment effects in patients with depression. However, social functioning disorder remains despite improvements in the depression symptoms (Hirschfeld et al., 2002). It has been suggested that improvements in social functioning are important for patients with depression to be able to adapt to society. Thus, social functioning is being taken into consideration in the treatment of patients with depression. Social functioning is instrumental to the quality of life, and it requires complex operations of various executive functions that include monitoring, reasoning, organizing, selecting, and planning. Depression and schizophrenia cause severe impairments in social functioning (WHO, 2004). Social functioning has received widespread attention as one of the most important outcomes in psychiatric disorders and has been related to cognitive functioning and the underlying brain activity.

The dysfunction of the prefrontal cortex (PFC) in patients with depression has been reported in previous studies that used neuropsychological tests (Beats et al., 1996; Degl'Innocenti et al., 1998; Moritz et al., 2002). This PFC dysfunction in patients with depression has been increasingly clarified by functional brain imaging

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http://dx.doi.org/10.1016/j.jpsychires.2015.01.009
0022-3956/

studies (Baker et al., 1997; Baxter et al., 1989; Drevets et al., 1997; Nobler et al., 2002; Okada et al., 2003, 2009). To date, it has been widely reported that cerebral blood flow and glucose metabolism are decreased in the dorsolateral prefrontal cortex and increased in the ventrolateral and ventromedial prefrontal cortex in patients with depression (Drevets, 2000). The medial prefrontal cortex has dense reciprocal connections with the amygdala and is presumed to inhibit the abnormally increased amygdala activity in patients with depression (Etkin et al., 2011). The medial prefrontal hyperactivity may indicate the need for stronger control in patients with depression compared to healthy controls. By contrast, lateral prefrontal area has primarily been associated with cognitive functions. However, recent studies suggest that the cognitive control functions may also pertain to emotion. Specifically, functional imaging studies demonstrate the recruitment of the lateral prefrontal area during the regulation of negative emotion through reappraisal/suppression strategies (Eippert et al., 2007; Levesque et al., 2003; Ochsner et al., 2002, 2004; Phan et al., 2005). Thus, a defect in the regulation of negative affect due to lateral prefrontal dysfunction is indeed a plausible mechanism for causing depression.

Multichannel near-infrared spectroscopy (NIRS), a functional neuroimaging technology widely used in recent years, can measure the hemodynamics over the surface of the cortices of the bilateral frontotemporal regions (Heinzel et al., 2013; Strangman et al., 2002a). This technique enables the detection of spatiotemporal characteristics of brain function by measuring the concentrations of oxy-hemoglobin (oxy-Hb) and deoxy-hemoglobin (deoxy-Hb), which are assumed to reflect the regional cerebral blood volume as demonstrated by good correlations with functional MRI (fMRI) signals (Sato et al., 2013). NIRS has several advantages over existing imaging techniques, such as positron emission tomography (PET), Single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI), because it is noninvasive, without using any radioactive substances, and is easy to administer, tolerates small movements, is inexpensive, and provides excellent time resolution (Ferrari and Quaresima, 2012). Meanwhile, it also contains disadvantages such as its poor spatial resolution, and the fact that it could not measure the deeper layer of the brain. Indeed, NIRS has been used to assess brain functions in many psychiatric disorders (Kameyama et al., 2006; Matsuo et al., 2003; Pu et al., 2008; Takizawa et al., 2014). In addition, NIRS was approved for application in clinical practice by the Ministry of Health, Labor, and Welfare of Japan in April 2009 as a clinical evaluation method for the differential diagnosis assistance of depression symptoms in psychiatric treatment in Japan. NIRS, which is a simple and noninvasive technique that can analyze the temporal course of brain function changes over a short period and in a natural position, allows for a relatively convenient examination that can be conducted in the outpatient clinic. In particular, it is a functional brain imaging examination that poses relatively little burden on elderly patients.

There have been several reports on the use of NIRS in patients with late-onset depression (LOD). A consistently reduced oxy-Hb activation in the PFC (hypoactivation) has been observed in patients with LOD according to NIRS findings in a study using a verbal fluency task (VFT) with the initial sounds of words, which is most commonly employed (Matsuo et al., 2000, 2005; Pu et al., 2008). However, there have only been a few reports on the connection between therapeutic responses in patients with LOD and NIRS findings. An objective diagnostic method for the prediction of depression treatment responses has yet to be established in other studies of neurological functional imaging as well.

There are still some debates as to what clinical aspects the NIRS signal actually reflects. One study by Noda et al. (2012) has demonstrated a significant negative correlation between NIRS signal activations in the frontal and right temporal regions and depression severity. However, in our previous study, we found a stronger cross-sectional correlation between NIRS signal activations in the PFC during the verbal fluency task and social functioning rather than the depressive symptom severity (Pu et al., 2008). In the present study, we performed pretreatment NIRS measurements in untreated patients with LOD and investigated the relationship between the treatment response of these patients, particularly the degree of improvement in social functioning, and the pretreatment NIRS findings. We hypothesized that pretreatment activity in the PFC is related to both pretreatment and degree of improvement in social functioning in patients with LOD.

2. Materials and methods

2.1. Participants (Table 1)

The subjects were 29 patients [7 males, 22 females, mean ± standard deviation (SD) age: 72.4 ± 5.71 years] who were diagnosed with major depressive disorder based on the DSM-IV (American Psychological Association, 1994) using the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998). None of the patients had clinical evidence of other central nervous system disorders based on medical history and examination. They visited the outpatients ward of Tottori University Hospital for the first time between September 2006 to July 2010 with an initial onset episode at an age of 65 years or older. The control group comprised of 29 healthy adults [7 males, 22 females, mean ± standard deviation (SD) age: 71.6 ± 5.57 years] matching the patients in terms of age and sex, with no history of neuropsychiatric diseases. The NIRS data of 7 out of 29 patients had been reported in our previous study (Pu et al., 2008) but not about their relationship with treatment response. All the patients with LOD were in a depressed mood state (Hamilton Depression Rating Scale [Hamilton Depression Rating Scale (HAM-D) score ≥15; 17 items; mean ± SD HAM-D score: 20.6 ± 5.22]. All the participants were right-handed with criteria of more than 80% by the Edinburgh

Table 1
Demographic and clinical variables of the participants.

Demographics	Patients (n = 29) (mean ± SD)	Healthy controls (n = 29) (mean ± SD)	t	df	Group difference
Age, years	72.4 ± 5.7	71.6 ± 5.6	−0.605	56	0.548
Gender, women/men	22/7	22/7	$X^2 = 0$	1	1.000
Handedness (%)	97.9 ± 6.2	97.9 ± 6.4	−0.042	56	0.925
Education, years	10.6 ± 1.9	11.6 ± 2.0	2	56	0.071
Estimated premorbid IQ	97.1 ± 12.4	92.6 ± 28.1	−0.782	56	0.437
Duration of illness, years	4.7 ± 5.6	–	–	–	–
Nuber of words generated	10.7 ± 3.9	12.2 ± 3.2	1.621	56	0.111
MMSE	27.5 ± 1.9	27.4 ± 2.4	−0.189	56	0.851
HAMD	20.6 ± 5.2	–	–	–	–
SASS	28.7 ± 9.8	41.0 ± 6.3	7.680	56	<0.001

Abbreviations: IQ, Intelligence Quotient; MMSE, Mini-Mental State Examination; HAMD, Hamilton Rating Scale for Depression; SASS, Social Adaptation Self-Evaluation Scale.

Inventory Index (Oldfield, 1971). All subjects gave their consent in a written form after receiving comprehensive information on the study protocol. The study was approved by the ethics committee of Tottori University Faculty of Medicine.

2.2. Assessments

Treatment with antidepressants was started for all patients, and symptom evaluations were conducted before and 8 weeks after the treatment (2 time points). Antidepressant choice was based on the judgment of the attending physician in the outpatient ward, and the dosage was increased to reach sufficient quantity within 4 weeks in all cases. The breakdown of the antidepressants used was paroxetine (10–40 mg) for 15 patients and milnacipran (50–150 mg) for 14 patients. Prior to NIRS measurement, all the subjects were assessed using Mini-Mental State Examination (MMSE) for their cognitive function and undertook self-assessments of social functioning: the Social Adaptation Self-evaluation Scale (SASS) (Bosc et al., 1997; Goto et al., 2005) scale was used. In addition, the patients were assessed for depression severity using the HAMD (Hamilton, 1960) by two trained psychiatrists (TY, KK).

2.3. NIRS measurements

2.3.1. Activation task

The task procedure in the present study was similar to that of Takizawa et al. (2008). Hb changes were measured during the VFT (letter version). The VFT was chosen, because it has been often used for cognitive activation in NIRS studies, and previous reports showed measurable prefrontal activation during the letter fluency task in healthy subjects (Herrmann et al., 2003, 2006; Kameyama et al., 2004; Pu et al., 2014). Each subject sat on a comfortable chair and was instructed to minimize movement such as head movements, strong biting and eye blinking during the NIRS measurements, so as to avoid artifacts.

The 160-s block-design VFT contains 3 different time periods: a 30-s pre-task period, a 60-s task period, and a70-s post-task period (Fig. 1). For the pre- and post-task baseline periods, the subjects were instructed to consecutively repeat the five Japanese vowels ("a", "i", "u", "e", "o") aloud. As readout from NIRS, the contrast between the verbal fluency condition and the vocalization condition was used to increase specificity for the verbal fluency. During the task period, they were instructed to generate as many Japanese words beginning with a designated syllable as possible. The three sets of initial syllables (A; /to/,/se/,/o/, B; /a/,/ki/,/ha/, C; /na/,/i/,/ta/) were presented in counterbalanced order among the subjects and each syllable changed every 20 s during the 60-s task. The total number of correct words generated during the VFT was adopted as a measure of task performance.

2.3.2. NIRS methodology

The 52-channel NIRS (ETG-4000, Hitachi Medical Co.) measures relative changes in oxy-Hb and deoxy-Hb using 2 wavelengths (695 and 830 nm) of infrared light based on the modified Beer–Lambert law (Yamashita et al., 1996). In this system, these Hb values include a differential pathlength factor (DPF). In addition, Zhao et al. (2002), using a Monte Carlo simulation, reported that the estimated DPF variation in the forehead region of adult humans was regarded as roughly homogenous. The distance between pairs of source-detector probes was set at 3 cm, and each measuring area between pairs of source-detector probes was defined as a "channel" (ch). The NIRS measures points at a depth of 2–3 cm below the scalp. This corresponds to the surface of the cerebral cortex (Okada and Delpy, 2003; Toronov et al., 2001). The probes of the NIRS were placed on the frontotemporal region of the participant, with the midcolumn of the probe located over Fpz, and the lowest probes were located along the T3-Fp1-Fpz-Fp2-T4 line in accordance with the international 10/20 system for electroencephalography. The arrangement of the probes enabled the measurement of Hb values from both prefrontal and temporal cortical surface regions (Fig. 2). The correspondence between the NIRS channels and the measurement points on the cerebral cortex was confirmed by a multi-subject study of anatomical craniocerebral correlation (Okamoto et al., 2004). The spatial information of each channel was estimated by using functions from the Functional Brain Science Laboratory at Jichi Medical University in Japan (http://www.jichi.ac.jp/brainlab/virtual_reg.html) (Tsuzuki et al., 2007).

The data sampling rate was 10 Hz. The obtained data were analyzed using the integral mode: the pre-task baseline was determined as the mean over a 10-s period immediately before the task period; and the post-task baseline was determined as the mean over the last 5 s of the post-task period. Linear fitting was applied to the data between these 2 baselines to reduce the effect of linear trend artifact. A moving average method using a window width of 5 s was applied to remove any short-term motion artifacts. Because we could not remove all artifacts in this way, we applied semi-automatic rejection of data with artifacts separately for each channel (Pu et al., 2012; Takizawa et al., 2008). (Number of channels, 33–52 [mean, 49.8; SD, 4.7]).

For the analysis of the hemodynamic response data, Hb variables for each channel were averaged for the both time segments (pre-task baseline and task period). We focused on oxy-Hb concentrations during the 60-s task period, since the oxy-Hb change (task period − pre-task baseline period) was assumed to more directly reflect cognitive activation than the deoxy-Hb change, as previously shown by animal studies and correlations with fMRI blood oxygenation level-dependent signals (Hoshi et al., 2001; Strangman et al., 2002b).

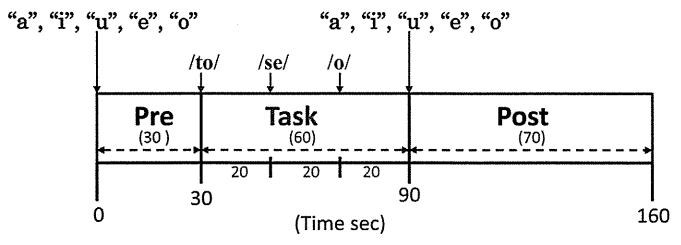

Fig. 1. The task design of verbal fluency test (VFT).

2.4. Statistical analysis

Statistical analyses were performed using SPSS Statistics 19.0 software (Tokyo, Japan).

First, we compared the patients group with healthy controls in terms of demographic data, MMSE and SASS scores using Student's t-tests and a chi-square test whenever appropriate. Next, we compared the NIRS activation (oxy-Hb) during the VFT between groups using a Student's t-test for each channel. In the case of multiple between-group comparison analyses for NIRS data, FDR correction was adopted to correct for the multiplicity of the analyses. Moreover, the relationship between pretreatment NIRS activation in each channel and the SASS score was analyzed using Pearson's product moment correlation analysis to confirm the cross-sectional relationship between the NIRS activation and the SASS score. We also tested the relationship between the pretreatment SASS score and the degree of improvement in the SASS score using Pearson's product moment correlation analysis in order to

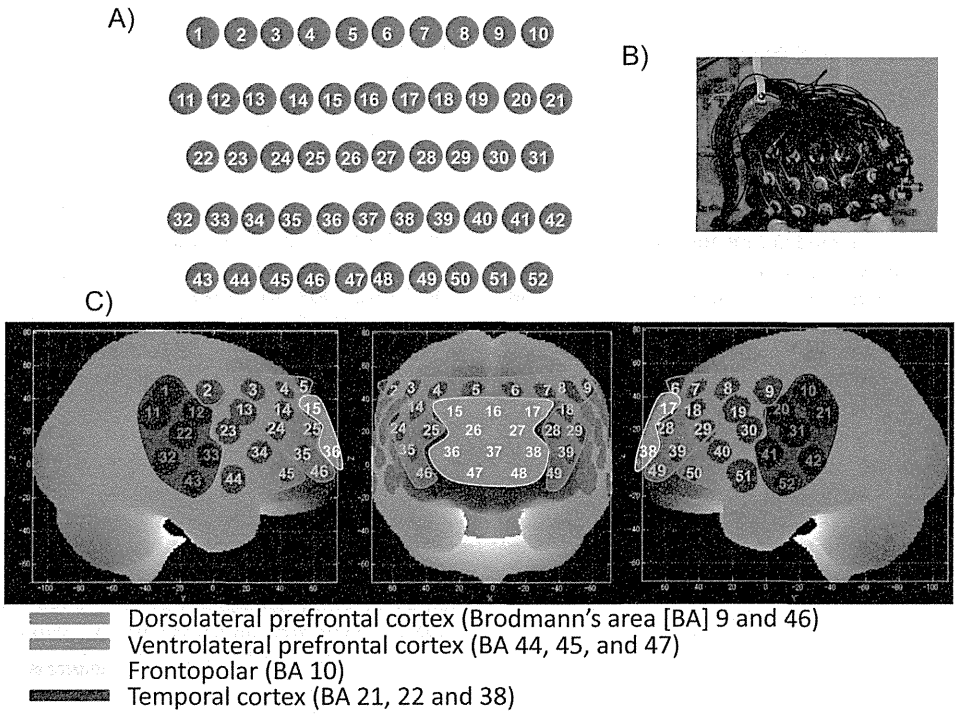

Fig. 2. Probe setting and measurement points for 52-channel near-infrared spectroscopy (NIRS). (A) The 52 measuring areas are labeled ch1–ch52 from the right posterior to the left anterior. (B–C) The probes with 3 × 11 thermoplastic shells were placed over a subject's bilateral prefrontal and superior temporal cortical surface regions. The channel numbers are indicated above the estimated cortical regions.

see whether the pretreatment SASS score may affect the degree of improvement.

Depression symptoms (HAM-D data) and social functioning (SASS data) pre- and post-8 weeks of after the treatment in the patients were compared with paired t-tests. With the objective of analyzing the relationship between pretreatment NIRS activation and clinical characteristics improvements due to treatment, particularly, the improvement in depression symptoms and social functioning, Pearson's correlation coefficient was calculated for each channel between the NIRS activation and the treatment-induced degree of improvement that was indicated by the SASS score. Moreover, in case there was a significant cross-sectional correlation between pretreatment NIRS activation and the SASS score, we performed additional partial correlation analyses between the degree of improvement in the SASS score and pretreatment NIRS activation data using the pretreatment SASS score as a control variable. A p value <0.05 was considered to be statistically significant. The multiplicity of the correlation analyses including NIRS data from 52 channels was not corrected, and therefore the results should be taken as exploratory.

3. Results

3.1. Between-group comparison

There was no significant difference between the groups in age, sex, educated years and MMSE scores, but the SASS score was significantly lower in the patients than the controls (Table 1).

The patients were associated with a significantly smaller NIRS activation than the controls at 33 channels (ch12, ch14, ch15, ch17, ch18, ch20, ch21, ch23 to ch29, ch31 to ch36, ch38 to ch46, ch49 to ch52; FDR-corrected p: 0.001–0.032), distributed predominantly in the ventrolateral and dorsolateral PFC, frontopolar, and temporal regions (Fig. 3).

3.2. Cross-sectional relationship between NIRS activation and the SASS score

The pretreatment NIRS activation in the area approximately located in the frontopolar and dorsolateral PFC was significantly correlated with the pretreatment SASS score (ch1, ch6, ch9, ch10, ch19 to ch21, ch25 to ch27, ch29, ch31, ch34, ch36, ch39, ch41, ch42, ch44, ch46, ch49, ch51, and ch52; R = 0.37 to 0.58; p = 0.001–0.048) (Fig. 5A).

3.3. Changes of depression symptoms and social functioning

A significant improvement in the HAM-D scores was observed between the two time points (pretreatment: 20.6 ± 5.22, posttreatment: 9.4 ± 7.37; t = 9.687, df = 28, p < 0.001). A significant improvement was also seen in the SASS scores (pretreatment: 28.7 ± 5.84, posttreatment: 35.5 ± 8.87, t = −4.716, df = 28, p < 0.001) (Fig. 4). There was no significant correlation between the pretreatment SASS score and the degree of improvement in the SASS score (R = −0.173, p = 0.369).

3.4. Relationship between pretreatment NIRS activation and the degree of improvement in depression symptoms and social functioning

Significant negative correlations between the degree of improvement in the SASS score after treatment and the pretreatment NIRS activation were observed in 8 channels (ch11, ch13, ch23, ch26, ch30, ch34, ch42, and ch44, R = −0.39 to −0.55; p = 0.0045–0.036) located approximately in the right ventrolateral PFC region (Fig. 5C). The pretreatment NIRS activation in any channel was not correlated with the degree of improvement in the HAM-D score after treatment (R = −0.24 to 0.31, n.s.).

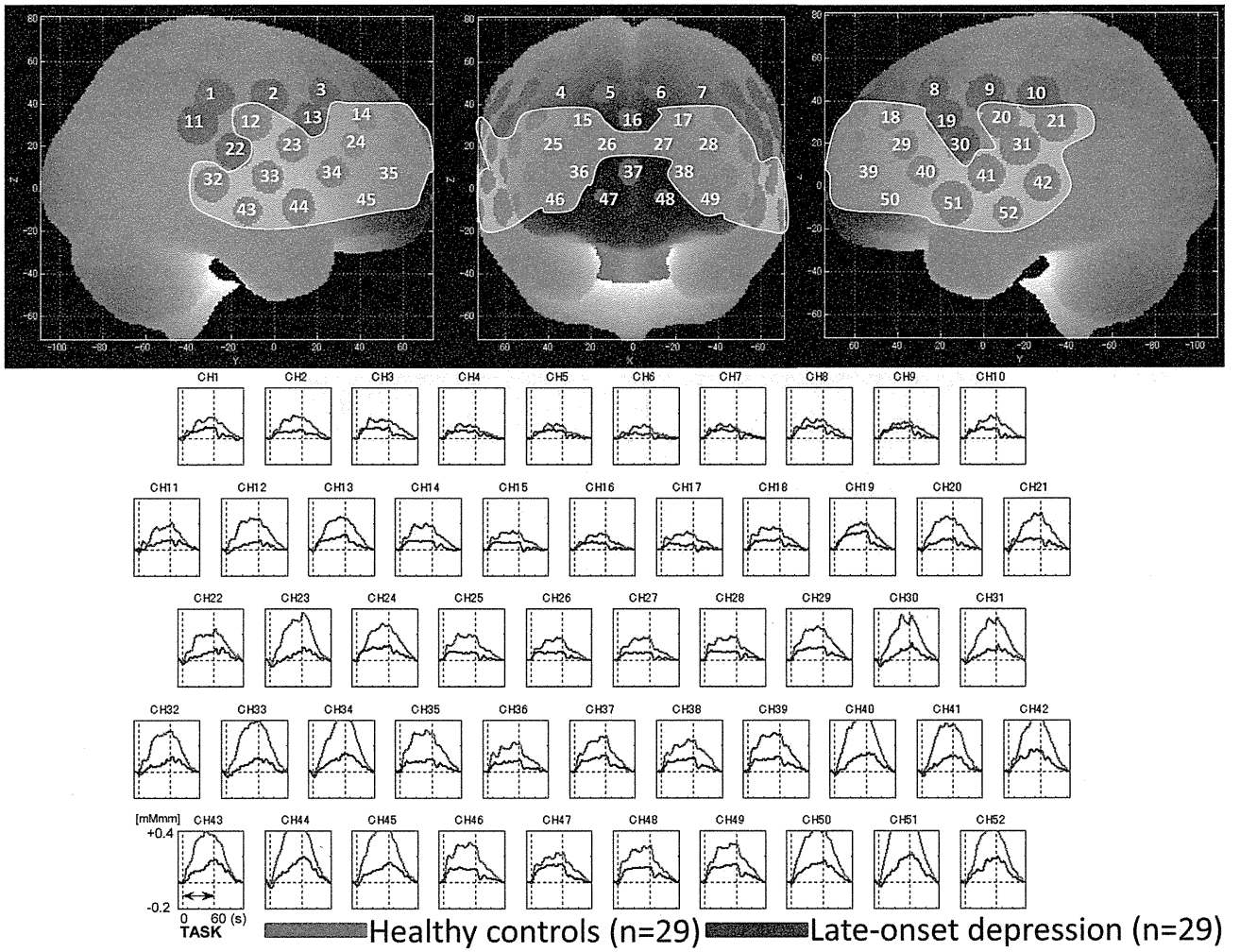

Fig. 3. Above: Brain area in yellow corresponds to the NIRS channels with significantly lower levels of activation in the LOD group than in the control group (FDR-corrected $p < 0.05$). The locations of NIRS channels were probabilistically estimated and anatomically labeled in the standard brain space in accordance with Tsuzuki et al. (2007). Below: Grand averaged waveforms of oxy-hemoglobin (oxy-Hb) during VFT (between two dotted vertical lines in each graph) in 52 channels over frontal and temporal regions measured by NIRS. Red and blue lines represent LOD and control groups, respectively.

As significant cross-sectional correlation analyses revealed significant relationship between the pretreatment SASS score and NIRS activation data in multiple channels located in the PFC, additional partial correlation analyses was conducted using the pretreatment SASS score in order to eliminate the effect of variance of pretreatment SASS score from the relationship between the degree of improvement in the SASS score and pretreatment NIRS activation data. Although the correlation between the pretreatment SASS score and the degree of improvement in the SASS score was not significant, a negative correlation coefficient ($R = -0.173$) suggest that it may have enhanced the negative relationship between the pretreatment NIRS activation and the degree of improvement in the SASS score to some extent. As a result, correlations between degree of improvement in the SASS score and pretreatment NIRS activation data remained significant in 6 channels mainly located in the right ventrolateral PFC (ch13, ch23, ch30, ch34, ch42, and ch44; $R = -0.43$ to -0.54; $p = 0.007$ to 0.024) (Fig. 5C).

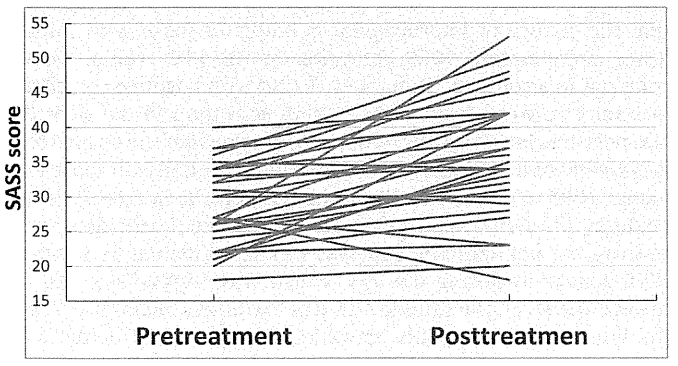

Fig. 4. SASS before and after treatment in patients with LOD.

4. Discussion

In this study, the pretreatment NIRS activation in the area approximately located in the frontopolar and dorsolateral PFC were positively correlated with the pretreatment SASS score; this is similar to our previous finding (Pu et al., 2008), whereas the pretreatment NIRS activation in the area approximately located in the right ventrolateral PFC was negatively correlated with the degree of improvement in the SASS score after 8 weeks of treatment. Our findings suggest the pretreatment NIRS activation not only