

2. MRI 撮像

fMRI は 1.5 Tesla の MRI 装置 (GE 社製) を用いて、AC-PC line に平行な 8 スライス (最下面は AC-PC line より 1 スライス下方) をスライス厚 7 mm (gap 1mm) で T2* 強調, gradient echo, echo planar imaging (EPI) シークエンスにより撮像した (TR = 3000ms, TE = 50ms, flip angle = 90°, FOV = 240mm, matrix = 64×64, voxel size = 3.75 × 3.75 × 7mm)。また fMRI 撮像終了後、位置同定のため全脳をカバーする 86 スライスの T1 強調シークエンスによる構造画像 (voxel size = 0.94 × 0.94 × 2mm) を撮像した。

3. 実験パラダイム

課題は、言語流暢性課題と対照課題を 30 秒ごとに交互に 3 回ずつ繰り返すブロックデザインとし、この間の脳活動を fMRI で測定した。言語流暢性課題においては被験者に対し 3 秒ごとに頭文字 (例えば 'た') を head coil 固定のモニターを通して視覚的に提示し、その頭文字で始まる単語を声には出さず頭の中で思い浮かべてもらった。対照課題では、被験者に対し 3 秒ごとに 'やすみ' と提示し、そのたびに 'やすみ' と頭の中で繰り返してもらった。また撮像終了後に言語流暢性課題における単語の産出数 ('た'、'て'、'さ'それぞれについて 30 秒間にできるだけたくさんの単語を言ってもらい、その数を合計) を測定した。

4. 統計解析

単語の産出数については、健常者群と患者群 (病相期)、健常者群と患者群 (寛解期)、患者群 (病相期) と患者群 (寛解期) を t 検定を用いて比較検討した。

fMRI によって得られた画像データは、解析用ソフトである SPM99 (Wellcome Department of Cognitive Neurology, London, UK) を用いて、前処理と統計解析を行なった。前処理として、各被験者の一連の脳画像の動きの補正と空間的標準化、3 次元 Gaussian-filter による smooting を行なった。統計解析は、被験者毎に血行動態反応関数 (HRF) を convolve した box-car 関数によって一般線形モデルに基づく統計的推定を行い、さらに課題条件-対照条件

の比較によってコントラスト画像を得た。続いて各被験者から得られたコントラスト画像を用いても検定によるグループ解析を行い、患者群 (病相期)、患者群 (寛解期) および、健常者群のそれぞれにおいて言語流暢性課題遂行中に対照課題遂行中と比較して有意に活動が上昇した領域 ($p < 0.001$ を有意として推定し、その空間的広がりを用いて多重比較の補正後 $p < 0.05$ を満たす領域) を同定し、比較検討を行なった。

結果

1. 神経心理学的評価 (単語の産出数)

言語流暢性課題における単語の産出数は、健常者群では平均±SD=26.4±7.2個、患者群 (病相期) では16.4±4.8個と患者群において有意に低下していたが、寛解期には21.9±3.3個と有意に改善した (Fig.1)。

2. fMRI で得られた局所脳活動

健常者群では先行研究に一致して言語流暢性課題遂行中に左前頭前野と視床および帯状回前部において有意な活動上昇が認められた (Fig.2)。一方、うつ病患者群 (病相期) においては帯状回前部では有意な活動上昇がみられず、左前頭前野では活動上昇はみられたものの、健常者と比較して賦活領域は減少していた (Fig.3)。また、患者群では症状改善後の測定においても帯状回前部の賦活はみられず、左前頭前野では病相期よりは広い範囲で賦活がみられたものの、健常者群と比較して賦活領域は減少していた。さらに、症状改善後の患者群のみ課題遂行時に右前頭前野の賦活がみとめられた (Fig4)。

考察

今回の研究から、うつ病患者では健常者と比較して左前頭前野や帯状回前部において言語流暢性課題遂行時の脳の賦活機能が低下していることが示唆された。この結果は、Tower of London 課題遂行中に帯状回前部の賦活がみられず、前頭前野の領域での賦活も健常者と比較し低下しているとする先行研究⁶と一致する結果であり、これまで報告されてきた安静時の血流低下と合わせて、うつ病患者でこれらの領域の機能異常があることを示唆するものであると考えられる。しかし、Wisconsin Card Sorting課題⁴ や Stroop 課題¹¹ を用いた先行研究では、うつ病患者で左前頭前野の賦活機能低下はみられないこ

とが報告されている。これらの不一致が、用いた課題による違いなのか、疾患の不均一性によるものなのかを明らかにするためには、今後同一患者において複数の課題を用いた検討を行なうなど、より詳細な検討が必要と考えられる。また、今回の縦断的研究の結果から、病相期にみられた左前頭前野や帯状回前部の賦活機能低下は、抗うつ薬による症状改善後も十分改善しないことが示唆され、継続療法の必要性を指示する結果と考えられた。さらに、寛解期の患者群でのみ右前頭前野において有意な賦活がみられたことから、神経心理学的評価では改善した後も、その基礎となる脳活動自体は健常者と異なっており、症状の再燃のしやすさや微細な認知機能の障害などと関連している可能性が考えられた。また、今回は少数例で短期間のフォローアップであったが、個々の症例では賦活機能の改善例もみられており、今後賦活機能の改善例と非改善例に分けて再燃のリスクなどを検討するなどさらなる縦断研究を行なうことで、fMRIを治療効果の判定や、抗うつ薬の減量、中止などの客観的な指標として応用していける可能性もあると考えられた。

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ストレスの適応の脳内メカニズム

The brain mechanism of an adaptation to stress

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抄録

われわれはストレス適応の脳内メカニズムを明らかにするために、脳機能画像解析法を用いた検討を行っている。本稿ではその研究成果を中心に報告したい。まずストレス事象がどこで認知されるかを明らかにするために対人関係ストレスに関連する単語の認知の機能局在に関する検討を行った。次にストレスが脳内機構に与える影響について明らかにするために急性ストレスの感覚入力系に及ぼす影響について検討した。最後に予測がストレスへの適応破綻の防止に有効であると考え、ストレス事象の予測に関する脳科学的検討を行った。その結果、ストレス事象は脳内において認知されること、急性ストレスにより脳内機構の一部に変化が生じること、予測がストレス事象の入力を抑制する可能性が考えられた。

Abstract

To clear the brain mechanism of an adaptation to stress, we have done neuroimaging studies used by fMRI and MEG. At first, to investigate which areas of the brain play an important role in the perception of stressful event, we performed a functional magnetic resonance imaging

(fMRI) study that involved recognition of unpleasant words concerning interpersonal relationships. Secondly, we evaluated the effect of various stress on sensory gating system by Magnetoencepharography (MEG), to show whether stress could affect in the brain mechanism. Finally, we studied the neural activity associated with the expectancy of emotional stimuli using fMRI and MEG, because of importance of expectancy in adaptation to stress. These results suggested that stressful events might be recognized in the some brain regions, that acute stress might affect one of brain mechanism, and that expectancy might suppress incoming stressful stimuli.

はじめに

人や動物が環境との相互作用の中で、過剰な環境の要求や苦痛な刺激にさらされたときに引き起こされるストレスの反応過程は、生理的反応とともに心理的過程を伴っている。特に人のストレスの反応過程を考える上では心理的な要因を抜きにしては考えにくい。人のストレス反応は心理社会的ストレスからもたらされることが非常に多いが、心理社会的ストレスは、それ自体が直接的にストレス反応を引き起こすのではなく、それがストレスとなるには、個人の認

知的な処理過程が必要である。

一方、生体がストレスに暴露されると、ストレス反応が生じるが、これはストレスがなくなると反応もおこらなくなる一時的な性質のものである。しかしストレスが慢性的あるいは、頻繁に繰り返される場合や、さらにストレスにさらされるのが一度の体験であっても、その記憶が意識に繰り返し侵入してくる場合など、ストレスへの適応が困難な状態が引き起こされる。脳での適応破綻の表現型が精神機能の障害であり、精神医学的見地からみると外傷後ストレス障害や大うつ病がこれに該当すると考えられる。従ってストレスに対する適応破綻の脳内メカニズムを解明することは、ストレス関連性精神障害の発症機序・治癒過程の解明にもつながり、現在その有病率の増大が懸念されているうつ病の治療法の改革にも寄与する重要な課題と思われる。

このような観点から、われわれはストレスの適応破綻の脳内メカニズムを明らかにするために、機能的磁気共鳴画像法(functional Magnetic Resonance Imaging:fMRI)と脳磁場計測法(Magnetoencephalography:MEG)といった脳機能画像解析手法を用いていくつかの検討を行っている。まずストレス事象がいかなる脳部位において認知されるかを明らかにするために対人関係ストレスに関連する単語の認知の機能局在に関する検討を行った。さらに、ストレス事象が脳内機構にどのような影響を与えるかを明らかにするために急性ストレスの感覚入力システムに及ぼす影響について検討した。最後に、ストレス事象の予測がストレスへの適応破綻の防止に有効であると考え、ストレス事象の予測に関する脳科学的検討を行った。本稿ではこれらの研究成果を中心に紹介したい。さらに、ストレス適応が破綻したモデルとしてうつ病を考え、これらの課題や手法を用いた研究も行っており、一部の結果をあわせて報告したい。

1.情動的ストレス単語の認知の機能局在

に関する検討1)2)

ストレスは一般的に物理的ストレスと心理的ストレスの2種類に分けることができる。物理的ストレスとしては熱、寒さ、密集(過密)、騒音などが知られ、心理的ストレスとしては対人関係上の葛藤、孤立(別離)などが知られている。心理的ストレスは精神疾患の発症の誘因となることが多く報告され、とりわけ対人関係に関連したストレスは大きな割合を占め、言語や表情を介して伝わっているものと考えられる。

対人関係に関連した刺激の認知に関する研究としては、表情の認知を用いた研究が多く行われている。それらの研究からは、扁桃核、尾状核や視床を含む基底核領域の活性化が知られている。しかしながら対人関係ストレスに関連する単語を刺激として用いた研究はなされておらず、情動的ストレスとなる言語がいかなる場所で認知されるかを明らかにすることは重要である。

健常者13例を対象に、1.5TのMRI装置(島津 Marconi 社製)を用い、emotional decision 課題遂行時のfMRIを撮像した。課題は、3語1組の対人関係ストレスに関連する負の情動価をもつ単語の中から最も不快な単語を選ぶ条件と、3語1組の情動的負荷を持たない中性の単語の中から最も中性な単語を選ぶ条件を交互に3回ずつ、計6ブロック繰り返した。1ブロック=30秒間に5組の単語セットを呈示する。被験者は各単語セットに対してボタン押しにて解答した。解析はSPM99を用い、対人関係ストレスに関連した単語呈示時と中性の単語呈示時の脳活動領域を比較検討した。課題終了後、各被験者は課題に使用した単語の主観的な不快さを点数評価した。

中性の単語呈示時と比較して、対人関係ストレスに関連した単語呈示時には左右尾状核、左視床、左海馬傍回が賦活された。さらに、左右尾状核、左視床の活動はストレスフルな単語の快適さの評価と逆相関をしていた。

この結果から、不快な単語刺激の認知

における左右尾状核、左視床の役割が示唆された。また、この領域の活動の強さは刺激の主観的な不快さの程度と関連しているものと考えられた。これまでの研究からは尾状核や視床は失望した表情の認知に関連していることが判っている。また、これらの部位の活動がストレスフルな単語を不快と評価した被験者ほど強かったことから、ストレスフルな言語の入力を調節する役割をもつ可能性が推定された。

2.急性ストレスの Sensory gating system に及ぼす影響³⁾⁴⁾

ストレス事象が脳内情報処理機構に与える影響を検討することは、ストレスへの適応を理解する上で極めて重要と考えられる。今回は、ストレスの認知する際の脳内情報処理機構の内、最初のコンポーネントにあたる感覚入力系 (Sensory gating system) に焦点をあて検討を行った。

Sensory gating system とは生体にとってあまり重要でない感覚刺激に対しては反応を小さくし (gating out)、重要な刺激に対しては反応を大きくする (gating in) 脳の前注意的な情報処理過程である。この情報処理過程は電気生理学的には、複数の事象関連電位によって構成されており、ストレスに対する適応機構として重要な役割を果たしていると考えられる。本研究では、ストレスに対する適応機構としての P50 suppression (gating out に対応) と Mismatch field (MMF; gating in に対応) に着目し、様々な急性ストレス負荷の影響について検討した。

健常者を対象としてストレス負荷前後に P50 suppression の変化を 204 channel 脳磁計を用いて測定した。P50 suppression は 500 ms 間隔で呈示される一対のクリック音 (1st, 2nd) を 8 秒間隔で提示し、クリック音に対する反応の強度の比 (2nd / 1st : t/c ratio) で評価した (t/c ratio が小さいほど gating out の能力が高い)。MMF は 500 ms 間隔で連続して呈示される標準刺激の中に 20% の割合で逸脱刺激を提示し、逸脱刺激に対する加算波形から

標準刺激に対する加算波形を引いた波形から MMF 反応を求めた。ストレスとしては、4口の氷水に1分間右手をつけるという物理的ストレス (cold pressor test) を負荷した。

健常者において cold pressor test は t/c ratio を増加させ、MMF 反応を増大させたのに対し、うつ病患者において t/c ratio は増加させたが、MMF 反応に対しては影響を与えなかった(図 1)。

すなわち、健常者で認められた急性の物理的ストレスに対する gating out は減少し、gating in は増加するという所見は、急性のストレス状況下では危機を事前に察知するための合目的な適応的な変化と考えることができる。しかしながら、そのストレスが一過性でなくストレス状況が遷延した場合や断続的に繰り返し曝された場合などでは、本来は感知されない刺激に曝され続けることを意味し、うつ病の発症要因としてのストレスの性質を考えていく上で興味深い。また、うつ病患者で物理的ストレスに対する gating in が認められなかったことから、健常者に認められた脳内情報処理の適応機構がうつ病患者では障害されている可能性が示唆された。

3.ストレス事象の予測に関する脳科学的検討⁵⁾⁶⁾

ストレスに対する心理的負荷を軽減するために、われわれはしばしば心理的な構えを準備する。例えば、結果が思わしくない場合に、結果発表の前に結果を予測し、これから受けるストレスを軽減するといったことを行うことがある。これらの心理的現象をふまえて、ストレス事象の予測がストレスの認知情報処理過程に大きな影響を与えていると考え、ストレス事象の予測に関する脳科学的検討を fMRI および MEG を用いて行った。

fMRI による検討は、健常者 15 例を対象に、1.5 T の MRI 装置(島津 Marconi 社製)を用い、予測的反応時間課題遂行時の fMRI を撮像した。課題は、二つ 1 組の刺激(警告刺激 S1 と標的刺激 S2)を一定の

刺激間隔(4sec)でモニターに呈示し、S2後にボタン押し反応をさせた。S1刺激として、○, □, ◻の幾何学図形を呈示した(100msec)。S2刺激として、異なる情動価(快/不快/中性; 各30枚)を持つスライドを呈示した(2sec)。被験者は、○-快、□-不快、◻-中性のようにS1-S2の組み合わせを固定した条件(予期可能条件)と、S1-S2の組み合わせがランダムな条件(予期不可能条件)を交互に行った。解析はSPM99を用い、予期可能条件と予期不可能条件の時の脳活動領域を比較検討した(図2)。

MEGを用いた検討は、健常者6例を対象に、全頭型204チャンネル脳磁図システム(Neuromag社製)を用い、予測的反応時間課題遂行時の脳磁図を記録した。被験者は、○-快、□-不快のようにS1-S2の組み合わせを固定した条件で、脳磁場データは情動価毎にS2呈示後1000msecを加算平均し、Visual evoked field (VEF)の脳内信号源の推定を行った(図4)。

予期可能条件では予期不可能条件と比較して、前頭前野の領域(内側前頭前野、下前頭前野、背外側前頭前野)で有意な活動上昇を認めた(図2)。

特に、快刺激を予測している時には、左背外側前頭前野、左内側前頭前野、右小脳の活動が認められたのに対し、不快刺激を予測している時には、右下前頭前野、右内側前頭前野、右扁桃、左前帯状回、および両側の視覚野(左右後頭葉、右嗅部、左舌状回)の活動がみられた(図3)。

さらに同じ課題を用いて情動スライド提示後の後頭葉視覚野に認められる反応の大きさの違いについて検討した。快および不快な情動スライド提示後に、後頭葉視覚野のほぼ同じ位置にVEFを認められたが、VEFの強度は、快刺激の予測と比較して不快刺激を予測したものでは小さかった(図2)。

これらの結果から、将来の情動ストレス事象の予測における前頭前野の役割、特に左前頭前野の活動と快刺激の予測および右前頭前野の活動と不快刺激の予測との関連が示唆された。また予測が視覚

野におけるネガティブな情報の入力を調節に関与していることが予想された。すなわち、ストレス事象を予測することにより、前頭前野を含む脳内ネットワークを介して、感覚野におけるストレスフルな入力を減弱させることが推測された。

おわりに

以上の健常人を対象としたfMRIおよびMEGを用いた検討から、ストレス事象は脳内において認知されること、急性のストレスにより脳内機構の一部に変化が生じること、予測がストレス事象の入力を抑制する可能性が考えられた。今後、うつ病を対象とした研究結果を踏まえて、ストレス適応破綻の脳内メカニズムや予防について脳科学的な観点から検討を行っていききたい。

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**Reduced activation of posterior cingulate cortex during
imagery in subjects with high degrees of alexithymia
: an fMRI study**

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Key words: alexithymia, imagery, posterior cingulate cortex, fMRI, future, happy

ABSTRACT

Background: Although the brain areas involved in imagery have been reported, the neural bases of individual differences in imagery remain to be elucidated. People with high degrees of alexithymia (HDA) are known to have constricted imaginal capacities. The purpose of this study was to investigate neural correlates of imagery disturbance in subjects with HDA.

Methods: A functional magnetic resonance imaging (fMRI) study was undertaken in 10 subjects with HDA and 10 subjects with low degrees of alexithymia (LDA), who were selected according to their scores on the 20-item Toronto Alexithymia Scale

(TAS-20). The authors compared the two groups' regional cerebral activation during various imagery conditions. In those conditions, the subjects imaged a past happy (PH) event, a past sad (PS) event, a past neutral (PN) event, a future happy (FH) event, a future sad (FS) event, and a future neutral (FN) event. The activation levels during these conditions were compared with that during a rest condition (REST).

Results: The t-tests showed that the mean subjective ratings of both the vividness of the imagery and the intensity of emotion during the imagery were higher in the subjects with LDA than in those with HDA for the PS and FS imagery conditions. On the other hand, relative to the LDA group, the HDA group showed significantly less activation in the posterior cingulate cortex (PCC) during the PH and FH imagery conditions than during the REST and during FH imagery condition than during FN imagery condition.

Conclusion: The present results suggest an association between a HDA and reduced activation of the PCC during happy imagery. Considering the function of this brain region, the results may be related to a dysfunction of episodic memory retrieval during happy imagery in subjects with HDA.

INTRODUCTION

The brain areas involved in imagery have been investigated by neuroimaging studies in normal subjects. These studies revealed that, in addition to primary and secondary sensory areas (Le Bihan et al 1993, Chen et al 1998, Cabeza and Nyberg 2000, Halpern 2001, Shergill et al 2001, Yoo et al 2003), brain areas with other major cognitive functions such as language, memory, and movement are activated during imagery (Mellet et al 1998). However, the neural bases of individual differences in imagery remain to be elucidated.

Alexithymia, a personality construct was introduced by Nemiah and Sifneos in the early 1970s. The concept evolved initially from clinical observations of patients with psychosomatic disorders (Nemiah et al 1976). The salient features of this construct are as follows: 1. difficulty identifying and describing subjective feelings; 2. difficulty distinguishing between feelings and bodily sensations of emotional arousal; 3. constricted imaginal capacities; and 4. an externally oriented cognitive style (Nemiah et al 1976). Recently, high prevalences of alexithymia have been reported in various psychiatric disorders, such as somatoform disorders (53% (Cox et al 1994); anxiety disorders (41% (Shipko et al 1983), 46.7% (Parker et al 1993); and substance dependence (51% (Taylor et al 1990)). An approximately 10% prevalence has been reported even in normal populations (Salminen et al 1999). Honkalampi et al 2000. Taylor (2000) stated in his review that alexithymia is a deficit in emotional regulation that reflects three kinds of deficits: a) deficits in the cognitive-experiential component of emotion response systems, b) deficits at the level of interpersonal regulation of emotion, and c) constricted imaginal capacities. Several studies have investigated imaginal

capacity in people with alexithymia. Nemiah et al (1977) reported that while controls increased their oxygen consumption when instructed to think various emotional thoughts, subjects with alexithymia showed no such increase in these conditions. While imaginal capacity correlates with hypnotic susceptibility (Varga2001), Frankel et al (1977) reported a high prevalence of alexithymia in subjects with low hypnotic susceptibility. Hyer et al (1990) studied the responses of PTSD patients who were listening to accounts of their own traumatic experiences, and found that the more alexithymic the subject was, the less his heart rate differed between the stressor period and the baseline. Friedlander et al (1997) compared the responses of people with alexithymia vs. those of people without it to an autogenic relaxation exercise with guided imagery; the former reported less enjoyment and poorer (less vivid) imagery during relaxation than did the latter. These studies suggest that people with High Degrees of Alexithymia (HDA) might have low imaginal capacities and show less physical reactivity during imagery with emotional contents. However, these studies relied on indirect methods to characterize the brain function of people with alexithymia.

Imagery can be defined as the manipulation of sensory information that comes from memory without information from actual sensory input . Cabeza and Nyberg 2000 . The memory is subdivided into working memory, episodic memory, and semantic memory. Of these subcategories, the one most closely tied to the emotions of daily life is episodic memory, especially "autobiographical memory" Rubin 1998 . Because alexithymia is conceptualized as a multifaceted construct consisting of factors related logically to each other . Taylor et al 1997 . , the imagery disturbance of alexithymia is considered to be related to other factors, such as difficulty in identifying and describing feelings, i.e., in processing

emotion. In fact, experimental studies suggest that imagery disturbance in subjects with alexithymia is related to emotion processing, as mentioned above. Thus, we considered that subjects with HDA might have difficulty in retrieval of autobiographical memory. On the other hand, the restricted imaginal capacities of people with alexithymia have been considered to limit the extent to which individuals with HDA can modulate anxiety and other emotions by fantasy, dreams, interest, and play . Krystal 1988, Myes and Cohen 1992 . . Thus, previous clinical reports have emphasized disturbances in imaging experiences that had not, and were not going to, occur as well as past experiences. Furthermore, in examining the types of emotion that accompany imaging, the previous reports seem to have emphasized the difficulty that people with alexithymia have in imaging positive things to modulate negative emotions such as anxiety. So, we planned an fMRI study to directly investigate neural correlates of imagery disturbance in the subjects with HDA using the imagery task in which subjects recall affect-laden autobiographical memories or imagine affect-laden future episodes accompanied by positive . happy . or negative . sad emotions.

Recent PET and fMRI studies have suggested that episodic memory retrieval is associated with activation of the prefrontal, medial-temporal, medial parieto-occipital . posterior cingulate cortex (PCC) including the retrosplenial cortex and precuneus . , lateral parietal, anterior cingulate, occipital, and cerebellar regions . Cabeza and Nyberg 2000 . . On the other hand, it has been reported that the retrieval of autobiographical memory, which is a kind of episodic memory, often activates the medial-frontal region and the left hippocampus, and sometimes activates the medial parieto-occipital cortex . Maguire 2001 . . These studies suggested a relatively

consistent activation of the prefrontal and medial-temporal cortices in episodic/autobiographical memory retrieval. However, there are also inconsistencies among studies of autobiographical memory retrieval, especially about the activation of the medial parieto-occipital area (MPOA). While several studies have reported the activation of this area . e.g., Maguire and Mummery 1999, Ryan et al 2001 . , a considerable number have reported no activation of this area . e.g., Markowitsh et al 1997, Conway et al 1999 . during the retrieval of autobiographical memory. Meanwhile, emotional stimuli have been reported to consistently activate this area . M addock 1999 . . Furthermore, while mental imagery is known to be a major component of episodic memory recall (Tulving 1983), MPOA in imagery domain studies seems to be specifically recruited whenever the generation of the mental image relies on the reactivation of a memorized percept (Kosslyn et al 1993, Mellet et al 1995, Roland and Gulyas 1995, Ghaem et al 1997). So both episodic memory recall and imagery might share the MPOA as a common region. We considered that the inconsistencies concerning the activation of MPOA across studies may reflect not only differences among tasks but also individual differences in personality traits . differences in individual patterns of reactions to emotional stimuli or in individual imaginal capacities . such as alexithymia. We therefore studied brain activity during imagery in volunteers and investigated the relationship between this brain activity and the level of alexithymia, while paying attention to MPOA (PCC and precuneus; Brodmann's areas 7, 23, 29, 30, 31). We hypothesized that the activation of the MPOA varies with the 20-item Toronto Alexithymia Scale (TAS-20) score during imagery, especially during emotional imagery conditions.

Meanwhile, although no study to date has used neuroimaging techniques to investigate the relationship between brain activation during imagery and alexithymic characteristics, two neuroimaging studies about alexithymia have recently been conducted (Berthoz et al 2002, Kano et al 2003). These studies suggested that there was no difference in the limbic structure between subjects with alexithymia and those without, and that the impairment of ACC functioning might be associated with alexithymia. Moreover, the medial prefrontal cortex (MPFC), adjacent to the ACC, also was activated in numerous neuroimaging studies of emotion (Phan et al 2002), and was reported to be impaired in subjects with alexithymia (Berthoz et al 2002). So, we were also interested in whether or not the ACC (Brodmann's areas 24, 32, 33) and MPFC (the medial regions of Brodmann's areas 8, 9, 10, 11) are associated with imagery disturbance in subjects with alexithymia.

METHODS AND MATERIALS

Subjects

We recruited 14 men and 6 women aged 20 to 30, who were right-handed, nonanxious, and nondepressed . based on Hospital Anxiety and Depression Scale scores . . Zigmond and Snaith 1983, Zigmond et al 1993 . , from among 38 male and 22 female volunteers according to their alexithymia scores on the Japanese version of the TAS-20. The volunteers were recruited through community announcements and were paid incentives corresponding to their transportation expenses. TAS-20 is the most psychometrically valid and commonly used measurement of alexithymia . Bagby 1994a, Bagby 1994b . , and the Japanese version also has high construct validity and reliability . Fukunishi et al 1997 . . It is a self-report questionnaire containing 20 items rated on a five-point scale. A high score

indicates HDA. According to Berthoz et al . 2002 . , 10 subjects (7 men and 3 women) with high (≥ 56) TAS-20 scores were placed into an HDA group; and 10 subjects (7 men and 3 women) with lower (≤ 44) scores, who were age- and handedness-matched to the HDA group, were placed into an LDA group. The subjects in the HDA and LDA groups were aged 25.9 ± 3.3 and 23.7 ± 3.0 years, respectively . mean \pm SD , and their TAS-20 scores were 61.9 ± 4.0 and 37.9 ± 3.9 , respectively . mean \pm SD .

All subjects were identified as right-handed according to the Edinburgh inventory . Oldfield 1971 . . According to the self-reported responses, the subjects had no history of psychiatric, neurological, or other major medical illness, and had never been treated with a psychotropic medication. After the study was described completely to the subjects, written informed consent was obtained from all of them. This study was approved by the Institutional Review Board and the Ethics Committee of Hiroshima University Hospital, Japan. The subjects received course credit for their participation.

Experimental Design

We developed our task by modifying that used in George et al . 1995 . . Before the scanning session, each subject was asked to name specific events that, when imaged, would make him or her happy . one past and one future event . or sad . one past and one future event . . Each subject was also asked to image a specific time when he or she was or would be emotionally neutral — that is, not experiencing any particular emotion . one past and one future event . . As for the future events, the subjects were asked to imagine, in the greatest possible detail, specific events that they could realistically expect to occur. The researcher then reviewed each event to assess whether or not the emotion was appropriate . e.g., not a mixture of happiness and sadness or anger to the type of event. Additional specific

sensory stimuli were elicited that could possibly aid in imaging the event . e.g., the exact place where the subject was or would be at the peak moment of emotion or the clothing, time of year, sights, sounds, or smells associated with that moment . . Finally each subject was asked to supply key words that would simply represent each event . e.g., travel with friends, death of grandmother, brushing teeth .

We used a periodic design involving the presentation of an activation condition for 30 seconds followed by a baseline condition for 18 seconds. This cycle was repeated 18 times over the course of 864 seconds. During the activation condition, subjects were cued by the visual presentation of Japanese words representing the six event conditions: “past happy” . PH . , “past sad” . PS . , “past neutral” . PN . , “future happy” . FH . , “future sad” . FS . , and “future neutral” . FN . ; key words were also used to cue the subjects to generate imagery of each event. When the words were presented, the subjects were instructed to image each previously agreed-upon event and to make themselves feel the emotions and senses that they would feel if the past or future event was actually happening. Each word was presented for 30 seconds. During the baseline condition . REST . , the subjects were shown a cross symbol . “ ” . and instructed to see only that symbol, with no imagery internally. Each presentation of the symbol was for 18 seconds. During each trial, the words were projected to the center of the subject’s field of view via an SVGA computer-controlled projection system. The order in which the activation conditions were presented was counterbalanced across the subjects. Each trial was started by presenting the cross symbol for 9 seconds; this initial presentation was excluded from the analyses. For each event, each subject’s ratings of the vividness of his or her imagery and the intensity of the emotion were recorded immediately after the scanning session. Two

nongraduated visual analogue scales were used: one assessed the vividness of the imagery (range, 0 to 10; from imaging nothing to imaging extremely vividly) and the other assessed the intensity of emotion during the imagery (range, 0 to 10; from feeling nothing to feeling extremely intense).

Image Acquisition

Functional MRI was performed using a Magnex Eclipse 1.5 T Power Drive 250 Shimadzu Medical Systems, Kyoto, Japan. A time-course series of 291 volumes was acquired with T2-weighted, gradient echo, echo planar imaging (EPI) sequences. Each volume consisted of 28 slices, with a slice thickness of 4 mm with no gap, and covered the entire cerebral and cerebellar cortices. The interval between successive acquisitions of the same image (TR) was 3000 ms, the echo time (TE) was 55 ms, and the flip angle was 90°. The field of view (FOV) was 256 mm and the matrix size was 64 × 64, giving voxel dimensions of 4 × 4 × 4 mm. Scan acquisition was synchronized to the onset of the trial. After functional scanning, structural scans were acquired using a T1-weighted gradient echo pulse sequence (TR = 12 ms; TE = 4.5 ms; flip angle = 20°; FOV = 256 mm; voxel dimensions of 1 × 1 × 1 mm), which facilitated localization.

Analysis

Image processing and statistical analyses were carried out using Statistical Parametric Mapping (SPM 99) software (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (Mathworks, Inc., Natick, MA). The first three volumes of the fMRI run were discarded because the MR signal was unsteady. The remaining 288 volumes were used for the analysis. Images were corrected for motion and realigned with the first scan of the session, which served as the reference. For each subject, the T1 anatomical images were coregistered to the first functional

images and aligned to a standard stereotaxic space, using the Montreal Neurological Institute (MNI) T1 template in SPM99. The calculated nonlinear transformation was applied to all functional images for spatial normalization. Finally, the functional MR images were smoothed with a 10-mm full-width at half-maximum (FWHM) Gaussian filter.

The group analysis was performed at two levels. At the first level, each subject's signal time course was modeled with a delayed box-car function convolved with a hemodynamic response function in the context of a general linear model. One contrast image per subject was created by contrasting each activation condition (PH, PS, PN, FH, FS, FN) with the baseline condition (REST) and by contrasting each emotional condition with the neutral condition. In the second step, using group analysis according to a random effect model, which allows inference to the general source populations (Friston et al 1999), we first identified regions that showed significant responses during each activation condition (PH, PS, PN, FH, FS, FN) compared to the baseline condition (REST) and during each emotional condition compared to the neutral condition (PH>PN, PS>PN, FH>FN, FS>FN) in the HDA and LDA groups, using the one-sample t-test. Next, the images were entered into a two-sample t-test (to locate brain regions in which the two groups differed significantly) and into a regression analysis (to locate brain regions in which the magnitude of brain activation correlated significantly with the TAS-20 score). Although there were inequalities in the amount of data between the REST condition and the experimental conditions (6 vs. 10), SPM 99 performed these analysis correcting the inequalities of data size. The resulting set of voxel values for each contrast constituted an SPM (T) map. The SPM (T) maps were then interpreted by referring to the probabilistic behavior of Gaussian random

fields. The data were thresholded at $p < 0.001$ uncorrected at the voxel level and at $p < 0.05$ corrected at the cluster level for regions about which there was no clear hypothesis. Moreover, for regions about which we had an a priori hypothesis (ACC, MPFC, and MPOA), the height and extent of thresholds were set to $p < 0.001$ uncorrected and $p < 0.05$ uncorrected, respectively (as justified by Friston 1997).

The x-, y-, and z-coordinates provided by SPM, which were in the MNI brain space, were converted to the x-, y-, and z-coordinates in Talairach and Tournoux's T T brain space. Talairach and Tournoux 1988. using the following formula: $TT-x = MNI-x \cdot 0.88 - 0.8$; $TT-y = MNI-y \cdot 0.97 - 3.32$; $TT-z = MNI-z \cdot 0.05 + MNI-z \cdot 0.88 - 0.44$. Labels for brain activation foci were obtained in Talairach coordinates using Talairach Daemon software. Research Imaging Center, University of Texas, San Antonio, TX, whose accuracy is similar to that of neuroanatomical experts. Lancaster et al 2000.

The accuracy of the labeling of the areas given by this software was then confirmed by comparison with activation maps overlaid on MNI-normalized structural MR images.

Results

Subjective Ratings

The t-tests showed that the mean subjective ratings of the vividness of the imagery were higher in the LDA group than in the HDA group for the PH, PS, and FS conditions. On the other hand, the mean subjective ratings of the intensity of emotion during the imagery were higher in the LDA group than in the HDA group for the PS and FS conditions. Table 1. The examples of the events, which subjects imaged during the imagery conditions, were sea bathing, party with friends, travel abroad; death of grand mother, death of dog, loss of bag; brushing teeth, cleaning, going to school; honeymoon,

playing with child, entrance to ideal occupation; death of mother, loneliness at work, failing to pass on to the next grade; washing face, changing clothes, driving for PH, PS, PN, FH, FS, FN conditions, respectively. There were no significant differences between the groups in the mean subjective remoteness of the time when the imaged event occurred or would occur, in any of the imagery conditions.

fMRI Results, brain activation during imagery conditions within groups

In the LDA group, at the higher level of significance height and extent thresholds, respectively, set to $p < 0.001$ and $p < 0.05$ corrected, there was significantly greater activation of the PCC in PH and FH than in REST, and of the left superior frontal gyrus in PS compared with REST. Moreover, at the lower level of significance height and extent thresholds, respectively, set to $p < 0.001$ and $p < 0.05$ uncorrected, the ACC and right precuneus were significantly more active in PN than in REST and in FH than in FN, respectively. In the HDA group, at the higher level of significance height and extent thresholds, respectively, set to $p < 0.001$ and $p < 0.05$ corrected, there was significantly greater activation of the fusiform gyrus and cerebellum in PH, PN, and FH than in REST (Table 2).

fMRI Results, comparison of brain activation between groups

With the threshold of significance at $p < 0.001$ uncorrected at the voxel level and at $p < 0.05$ corrected at the cluster level, FH compared with REST induced less activation in the HDA subjects than in the LDA in the bilateral PCC. Table 3, Figure 1. These were the only regions showing between-group differences at this level of significance.

Moreover, at the lower level of significance height and extent thresholds, respectively, set to $p < 0.001$ and $p < 0.05$

uncorrected. , PH compared with REST and FH compared with FN induced less PCC activation in the HDA group than in the LDA (Table 3, Figures 2, 3)

fMRI Results (regression analysis)

Regression analysis revealed a significant inverse correlation between the TAS-20 score and the magnitude of brain activation of the bilateral PCC in PH compared with REST ($x,y,z=-6, -54, 9$; area 30; t -value 5.26; 1595 voxels; $r=-0.846$; $p<0.001$), in FH compared with REST ($x,y,z=-8, -50, 9$; area 30; t -value 7.83; 1363 voxels; $r=-0.810$; $p<0.001$), and in FH compared with FN ($x,y,z=6, -62, 21$; area 31; t -value 6.52; 669 voxels; $r=-0.812$; $p<0.001$) at the higher level of significance height and extent thresholds, respectively, set to $p<0.001$ and $p<0.05$ corrected. . The Talairach coordinates presented in each parenthesis represents the coordinates in which the local maximum within the cluster was observed. No significant correlation was observed in any other investigated contrasts.

DISCUSSION

As expected, the activation of the MPOA varied with the TAS-20 score the degrees of alexithymia during imagery. During FH imagery, the activation in the PCC was significantly lower in the HDA subjects than in the LDA. Also in FH imagery, a significant inverse correlation was found between the TAS-20 score and the magnitude of PCC activation. These results support our hypothesis that the inconsistencies about the activation of MPOA across studies reflect individual differences in personality traits such as alexithymia. The variability of activation in this area according to alexithymic characteristics may explain why prior studies, which did not control for personality, reported various outcomes.

A qualitative comparison of the brain activation detected by one-sample t -test in the two groups suggests other findings in

addition to the intergroup difference in PCC activation. The LDA group showed significantly greater activity of the MPFC, which also extends to the ACC, during PS imagery, but the HDA group did not. This is partially in line with the ACC deficit model of alexithymia (Lane et al 1997, Berthoz et al 2002). There seems to be greater activation in the fusiform gyrus and cerebellum in the HDA group than in the LDA, which might reflect visual attention (Mangun et al 1998, Allen et al 1997). However, such a comparison does not allow us to measure voxel-by-voxel differences in the magnitude of activation between the groups. A more formal test of the null hypothesis of no between-group difference in activation was provided by a two-sample t test at each voxel. A direct comparison between the groups showed significantly lower brain activation in the PCC of the HDA group than the LDA during FH imagery.

There is considerable evidence that the PCC has functions related to episodic memory (Andreasen et al 1995, Grasby et al 1993, Henson et al 1999, Maddock et al 2001) . A review of functional imaging studies showed that the caudal part of the PCC was the cortical region most consistently activated by emotional stimuli compared to nominally matched, emotionally neutral stimuli (Maddock 1999) . Moreover, it has been speculated that the PCC plays a role in the modulation of memory by emotionally arousing stimuli (Maddock 1999) .

The PCC has strong, reciprocal connections with regions engaged in memory processing, such as medial-temporal lobe memory structures and the thalamus (Bentivoglio et al 1993, Suzuki and Amaral 1994). It is also reciprocally connected to regions engaged in emotional processing, such as the ACC and the orbitofrontal cortex (Goldman-Rakic et al 1984, Musil and Olsen 1993, Van Hoesen et al 1993) . These neuroanatomical findings

also suggest the PCC is involved in both memory and emotion. It is especially interesting that the ACC and PCC are connected reciprocally whereas recent neuroimaging studies have suggested that the ACC has neural correlates of alexithymia (Berthoz et al 2002, Kano et al 2003). Although in our imagery task the activation of the ACC is not related to the degrees of alexithymia, the disturbance of both the ACC and PCC may compose the various features of alexithymia, having interaction.

One possible explanation for the difference between the groups in brain activation during FH imagery is that people with HDA can construct FH imagery, but in a different way than people with LDA do. It is known that the primary and secondary sensory cortices, such as the visual or auditory cortex, are activated during imagery (Cabeza and Nyberg 2000, Shergill et al 2001). But the activation of these areas did not significantly differ between subjects with HDA and subjects with LDA in any of the imagery conditions. So, we can't consider that people with HDA are less imaginal, at least on the sensory level. Together with the function of the PCC mentioned above, our results indicate that subjects with LDA use memories of past emotional events to create FH imagery, but subjects with HDA rarely or never do. On the other hand, the evaluation of an emotionally salient stimulus engages a variety of cognitive processes, many of which have been considered to rely on episodic-memory retrieval (Pratto 1994). Another explanation is that the activation of the PCC is associated with the evaluation of emotional stimuli that depend on episodic memories, and subjects with HDA evaluate their FH imagery as less exciting than do subjects with LDA.

Moreover, the BOLD response presented during PH and FH imagery compared with REST suggests a deactivation of the PCC in the HDA group.

Recently, functional imaging studies have shown that certain brain regions, including the PCC, consistently show greater activity during resting states than during cognitive tasks. Furthermore, it has been hypothesized that these brain regions constitute a default mode network (Raichle et al 2001, Greicius et al 2003). Raichle et al (2001) speculated that in the default state, information broadly arising in the external and internal milieu is gathered and evaluated, and that when focused attention is required, activity within these areas may be attenuated. The HDA group demonstrated significant activation in the fusiform gyrus and not in the PCC, whereas the LDA group demonstrated the reverse pattern of activation in the one-sample t-test. The fusiform gyrus is related to visual attention (e.g. Mangun et al 1998). Together with the external oriented cognitive style of alexithymia (Nemiah et al 1976, Taylor et al 1997), we speculated that because the HDA subjects might have been more engaged in visual attention to displayed cue letters than in the retrieval of episodic memory, deactivation of the PCC might have been greater in subjects with HDA than in those with LDA, and the deactivation might likely contributed to the between-group results.

At a lower level of significance, the PCC was less active in the HDA group than in the LDA during the PH imagery condition compared with REST. These results, together with the result of the group comparison in FH>REST, FH>FN contrasts, suggest that it is difficult for individuals with HDA to imagine happy events. Our results support the previous researchers' speculation that the restricted imaginal capacities of people with alexithymia limit the extent to which individuals with HDA can modulate negative emotions by imaginative activities that have positive connotations, such as fantasy, dreams, interest, and play (Krystal 1988, Mayes and Cohen 1992). According to Bagby et al (1994b), within the

correlation between the TAS-20 and the subscales of Extraversion, alexithymia was associated significantly and negatively with the tendency to experience positive emotions. Our data support their idea that alexithymia is associated with a low proneness to experience positive emotions. However, in the PH>PN contrast, there was no significant difference between the groups. Our subjects usually chose daily acts as PN events, and these events were often more recent and more familiar than PH events. Meanwhile, the recency (Pifke et al 2003) and familiarity (Kosaka et al 2003) of autobiographical memory seem to increase PCC activity. The recency and familiarity of PN events might have confounded and diminished the difference between PH and PN conditions in the activation of PCC. To reach a conclusion about the difference in happy imagery between these two groups, further studies controlling these factors are needed.

There is another possible explanation of why the groups differed significantly only in the FH imagery condition. That is, our results may support the previous researchers' speculation that individuals with HDA find it hard to imagine something that they have never experienced. Clinical observations suggest that individuals with HDA seem to be swayed too much by minutiae of superficial, "external" things and can't imagine invisible, intangible things such as mental content or the future (Marty and M'Uzan 1963, Taylor et al 1997). They can recall intact their past experience, but they can't process their experience or imagine events they have never experienced. However, our results suggested that the groups did not differ from each other in the FS and FN imagery conditions compared with REST. For FN events, our subjects usually chose daily acts that they had already experienced. We consider that this may explain why the groups did not differ in the FN condition. Moreover, although we did not discuss this in the Results section, the

PCC was less active in the HDA group than in the LDA during FS compared with REST and in FS compared with FN (number of voxels in cluster : 96 and 97, respectively) when the threshold was set at an uncorrected $p < 0.001$ at the voxel level in an a priori hypothesized region (Elliott et al 2000). On the other hand, there was no difference between the groups in PCC activation during PS compared with REST or during PS compared with PN, even at this lower threshold.

Meanwhile, discrepancies were observed between brain activation and subjective rating results. In general, the different responses to sad and happy imagery conditions were as follows. There were no significant differences in brain activation between the HDA and LDA groups in sad imagery conditions, but there were such differences in subjective ratings between the groups. For happy imagery conditions, on the other hand, the opposite was found: there were no significant differences between the groups in subjective ratings, but such differences were found in brain activation. These results seem to be paradoxical. We speculate that there were no significant differences between the groups in brain activation during sad imagery in the scan, but there might have been differences between the groups in brain activation when the subjects reported the subjective ratings after the scan. Several investigators suggested that alexithymia may involve a "decoupling" of the subjective and physiological components of the emotional response to stressful stimuli — that is, a higher degree of alexithymia was associated with fewer subjective responses and greater physiological reactivity (Papciak et al 1985, Martin and Pihl 1986). The results of these previous studies may suggest that subjects with alexithymia have deficiencies in conscious awareness of emotion. In previous neuroimaging studies of alexithymia, the ACC and MPFC have been reported as the

neural correlates of conscious awareness of emotion. Studies about decoupling theory have focused exclusively on negative emotion. Berthoz et al (2002) reported that the activation of the ACC/MPFC was lower during negative stimuli and higher during positive stimuli in people with alexithymia than in people without it. Kano et al (2003) found that although the activation of ACC was lower in subjects with alexithymia than in those without it in response to an angry face, there was no difference between groups in the ACC activation in response to a happy face. These results also suggest that “decoupling” occurs in relation to negative emotion but not to positive emotion. If so, when brain activations differ between HDA and LDA subjects during happy imagery, subjective ratings should also differ between HDA and LDA subjects. In this study, however, no significant differences were found in subjective ratings of intensity of emotion during the happy imagery conditions. This might have been influenced by the difference in effect size between brain activation and subjective rating. Neuroimaging is a much more powerful tool than traditional behavior methods for detecting subtle relationships between two variables (Canli and Amin 2002). In fact, in spite of the small sample size, subjective ratings of the intensity of emotion tended to be higher in the LDA group than in the HDA for PH and FH, although not significantly.

On the other hand, to our surprise, there was no significant difference in the activation of the ACC/MPFC region between the groups for which we had an a priori hypothesis. The small sample size may explain the absence of such a difference. In fact, a qualitative comparison of brain activation by the one-sample t-test suggested that the LDA group had significantly greater activity than the HDA in the ACC/MPFC region during PS imagery. Second, if the subjects with HDA had poorer imaginal capacity than those with LDA, the activation

of this area during the control condition, that is REST condition (during which free recall could occur) and the neutral imagery condition, could be greater in the LDA group. In fact, ACC activation in the LDA group was significantly greater in PN than in REST in this study, while no ACC activation was found in the HDA group during PN.

Furthermore, the brain activity detected by the one-sample t-test was poorer than it was in George et al (1995), which showed bilateral limbic and paralimbic activation including that of the ACC/MPFC. We considered that factors such as the shorter time interval among tasks, which may have resulted in mutual influence, or the shorter duration of imagery generation in this study than in the PET study of George et al (1995), may have influenced these differences in results between the two studies. Next, no difference between the groups was observed in the limbic structure (i.e., the amygdala, the hippocampal formation, and the hypothalamus), which plays a central role in emotional responses to simple perceptual aspects of stimuli. This finding is consistent with previous studies that found that the limbic area is not associated with alexithymia (Berthoz et al 2002, Kano et al 2003). Furthermore, no difference between the groups was observed in the insular cortex or in the orbitofrontal cortex; these cortices have been discussed in numerous neuroimaging studies about emotional recall/imagery (Phan et al 2002) and general emotional processing (Bechara et al 2000), respectively. This absence of activity may be attributable to the imaging method used. While activation of these regions has been reported mainly in PET studies, it is known to be difficult to detect the activation of these areas by fMRI for susceptibility artifact (Ojemann et al 1997). Thus, our study can't conclude that there is no relationship between emotional imagery disturbance related to alexithymia and these important

brain regions, except for the PCC. Further studies considering these points are needed.

There are some limitations to this study. First, because of the small sample size, we may have failed to identify activation differences between HDA and LDA in other imagery conditions. Second, the sensory modalities of imagery (auditory, olfactory, etc.) involved in each event, in addition to visual sensation, differed not only between subjects but within each subject. This may have been a confounding factor. However, it is difficult to control these factors because autobiographical memory is usually multi-modal, and because imagery, in which sensory modality is restricted, is different from daily experiences, especially emotional ones. Third, the subjects' retrospective ratings of their imagery and intensity of emotion may have been inaccurate, especially if the subjects with HDA had trouble with episodic memory. Finally, some subjects may have been unable to refrain from imagery and emotion or other cognitive activity during the rest periods. The level of each subject's cognitive activity during these rest periods may also be a confounding factor. Further studies considering these points are needed.

In conclusion, the present study revealed that the reduced activation of PCC in subjects with HDA was associated with the disturbance of FH imagery. The disturbance of FH imagery can reduce motivation and hope, and it may be an important factor in the construction of deficits in the emotional regulation of alexithymia. We suggest that PCC may play a crucial role in alexithymia-related imagery disturbance. Although this study has several limitations, the present results are meaningful as the first report to demonstrate neural correlates of imagery disturbance in alexithymia.

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