表6 痛み動画＞コントロール動画のコントラスト

| | area | BA | MNI x | MNI y | MNI z | T | Z | Cluster k |
|---|---|---|---|---|---|---|---|---|
| Right | Inferior Temporal Gyrus | | 54 | −70 | −4 | 23.74 | 5.72 | 3215 |
| Right | Middle Occipital Gyrus | | 34 | −92 | −4 | 11.45 | 4.67 | |
| Right | Inferior Temporal Gyrus | | 44 | −72 | −4 | 11.07 | 4.61 | |
| Left | Inferior Parietal Lobule | 40 | −62 | −40 | 32 | 19.68 | 5.47 | 3232 |
| Left | Inferior Parietal Lobule | 40 | −34 | −46 | 42 | 14.82 | 5.06 | |
| Left | Postcentral Gyrus | 2 | −48 | −30 | 42 | 12.92 | 4.85 | |
| Right | Thalamus Lateral Dorsal Nucleus | | 12 | −20 | 14 | 18.44 | 5.37 | 236 |
| Right | Thalamus Ventral Lateral Nucleus | | 14 | −14 | 8 | 10.13 | 4.47 | |
| Right | Thalamus Ventral Posterior Medial Nucleus | | 16 | −24 | 2 | 10.1 | 4.47 | |
| Left | Inferior Frontal Gyrus | 9 | −58 | 8 | 34 | 18.09 | 5.35 | 1025 |
| Left | Precentral Gyrus | 6 | −50 | 4 | 12 | 9.39 | 4.35 | |
| Left | Precentral Gyrus | 44 | −58 | 10 | 14 | 9.05 | 4.29 | |
| Left | Putamen | | −24 | −4 | 4 | 16.62 | 5.23 | 296 |
| Left | Putamen | | −32 | −18 | −2 | 7.87 | 4.06 | |
| Left | Insula | 13 | −40 | −4 | 10 | 7.04 | 3.87 | |
| Left | Middle Temporal Gyrus | 37 | −46 | −62 | 2 | 15.61 | 5.13 | 3650 |
| Left | Inferior Occipital Gyrus | 19 | −34 | −78 | −12 | 13.71 | 4.94 | |
| Left | Inferior Occipital Gyrus | 18 | −32 | −94 | −16 | 12.91 | 4.85 | |
| Left | Medial Frontal Gyrus | 6 | −6 | −2 | 62 | 14.84 | 5.06 | 503 |
| Left | Superior Frontal Gyrus | 6 | −4 | 6 | 54 | 10.06 | 4.46 | |
| Right | Medial Frontal Gyrus | 6 | 4 | −6 | 64 | 9.26 | 4.33 | |
| Right | Postcentral Gyrus | 2 | 48 | −32 | 40 | 13 | 4.86 | 454 |
| Right | Inferior Parietal Lobule | 40 | 40 | −38 | 36 | 8.21 | 4.13 | |
| Right | Inferior Parietal Lobule | 40 | 56 | −22 | 26 | 7.08 | 3.88 | |
| Left | Middle Frontal Gyrus | 46 | −50 | 30 | 26 | 12.78 | 4.84 | 251 |
| Left | Middle Frontal Gyrus | | −50 | 36 | 18 | 6.23 | 3.66 | |
| Left | Middle Frontal Gyrus | 10 | −38 | 36 | 28 | 5 | 3.27 | |
| Right | Superior Parietal Lobule | 7 | 14 | −64 | 66 | 11.12 | 4.62 | 544 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Right | Superior Parietal Lobule | 7 | 28 | -62 | 62 | 10.52 | 4.53 | |
| Right | Superior Parietal Lobule | 7 | 20 | -72 | 58 | 8.63 | 4.21 | |
| Left | Thalamus Mammillary Body | | -10 | -22 | 2 | 9.92 | 4.44 | 156 |
| Left | Thalamus Lateral Posterior Nucleus | | -16 | -20 | 12 | 5.61 | 3.48 | |
| Left | Thalamus Medial Dorsal Nucleus | | -8 | -14 | 8 | 5.3 | 3.38 | |
| Left | Superior Frontal Gyrus | 9 | -4 | 60 | 34 | 8.8 | 4.24 | 15 |
| Right | Precentral Gyrus | 6 | 42 | -6 | 46 | 8.35 | 4.16 | 173 |
| Right | Middle Frontal Gyrus | 8 | 48 | 8 | 46 | 6.91 | 3.84 | |
| Left | Middle Frontal Gyrus | 6 | -28 | -8 | 58 | 8.01 | 4.09 | 694 |
| Left | Middle Frontal Gyrus | 6 | -42 | 0 | 50 | 7.65 | 4.01 | |
| Left | Middle Frontal Gyrus | 6 | -26 | -10 | 48 | 7.56 | 3.99 | |
| Right | Precentral Gyrus | 44 | 58 | 14 | 8 | 7.77 | 4.04 | 195 |
| Right | Inferior Frontal Gyrus | 45 | 58 | 24 | 2 | 7.34 | 3.94 | |
| Right | Inferior Frontal Gyrus | 47 | 56 | 38 | -4 | 6.69 | 3.78 | |
| Right | Superior Frontal Gyrus | 6 | 30 | -4 | 68 | 7.56 | 3.99 | 70 |
| Right | Sub-Gyral | 6 | 24 | -4 | 54 | 7.22 | 3.91 | |
| Right | Cerebellum Inferior Semi-Lunar Lobule | | 20 | -72 | -50 | 7.35 | 3.94 | 66 |
| Right | Cerebellum Inferior Semi-Lunar Lobule | | 10 | -76 | -50 | 5.61 | 3.48 | |
| Left | Superior Frontal Gyrus | 10 | -38 | 50 | 26 | 6.26 | 3.67 | 44 |
| Left | Inferior Frontal Gyrus | 47 | -38 | 30 | -12 | 5.94 | 3.58 | 30 |
| Right | Inferior Parietal Lobule | 40 | 46 | -40 | 60 | 5.52 | 3.45 | 64 |
| Right | Postcentral Gyrus | 5 | 34 | -46 | 68 | 5.43 | 3.42 | |

### C.3. リアルタイム fMRI(rtfMRI)の導入・プログラム開発

リアルタイム f MRI に必要なフィードバック解析システムを、米 MIT と協力し、Matlab をベースにしたプログラミングによって構築し、動作確認を行った。先にリクルートした健常群を対象に、1.5T-MRI を用いて、EPI シークエンスによる fMRI 撮像中に情動刺激を与え、個々人において、該当する脳活動領域を改めて確認し、同じ課題を与え、その脳領域の BOLD 信号を撮像と同時にその場で抽出し即時に解析し、その脳活動の値を、fMRI

撮像中の被験者に視覚的にわかりやすく提示する(自動車のメーターの絵)ためのシステムをプログラム作成し、関心領域の脳活動が得られた後、約0.8 秒で解析を終えることができることを確認した。

D．考察

恐怖症などの不安障害における感情調節機構の障害特性とその責任脳領域を明らかにし，rtfMRIを用いたニューロフィードバックによるコントロールへ臨床応用していくために，本研究では健常者を対象として感情喚起刺激であるIAPSと、痛み動画刺激の妥当性の確認を行った。
その結果，これまで多くの研究者によって行われてきた情動刺激を用いた脳機能イメージング実験と同様の脳活動が観察された(Hariri et al., 2003, Sabatinelli et al., 2005)。

まず，IAPSを用いた研究では、感情条件（不快，快）に特有な脳活動として扁桃体の賦活が認められた。これらの活動は各条件の画像による感情生起に関連していたと考えられる。

感情刺激の処理と扁桃体の活動に関しては数多くの研究が行われてきた。そして，それらの研究から，1）扁桃体は様々な感覚モダリティからもたらされる不快刺激に応答し，2）快刺激にも応答するがその応答には不快刺激によって引き起こされるほど一貫性がなく，3）応答性は刺激の覚醒度（arousal level），快の強さ（hedonic strength），そして刺激がその時に持つ動機付けの価値（motivational value）によって修飾され，4）応答性は急速に馴化し，5）時間応答は刺激の種類や被験者（健常者，患者など）によって変化し，6）扁桃体の活動は意識的な気づきがなくとも生じ，7）意識的な快の評価に扁桃体の活動は必要ではなく，8）扁桃体の活動は運動準備性，自律神経活動，記憶や注意といった認知プロセスの修飾に関連し，9）活動の左右差に関しては伝統的な感情の側性化モデルには従わず，10）活動の大きさや左右差は精神状態，性別，性格などの要因と関連していることなどが明らかにされてきた(Zald, 2003)。

また，両側の扁桃体と下側頭皮質（紡錘状回含む）のBOLD signalの大きさは，感情刺激の覚醒度（arousal）に比例して増大し，覚醒度の高い画像を見ているときのBOLD signalは中性画像に比べて倍増することが知られている(Sabatinelli et al., 2005)。本研究でも，不快条件における両側扁桃体の活動は，快条件，中性条件に比べて約二倍に増大していることが示された。
腹側視覚経路は扁桃体と密な線維連絡を有しているため，感情的な視覚刺激知覚時の紡錘状回の高い活動は，動機づけられた対象への注意の高まりに関連していると考えられている(Sabatinelli et al., 2005)。

これらをまとめると，扁桃体の活動は刺激の重要性（salience）を自動的に評価し，その評価に基づいて速やかに他の脳領域の活動を修飾することであると考えられる(Ewbank, Barnard, Croucher, Ramponi, & Calder, 2009)。恐怖症における，扁桃体が担うこの生物学的に重要な機能に変化が見られるかを評価する

ためにも，IAPS を感情喚起刺激として用いることの可能性が本研究結果によって確かめられた。

さらに，不快条件に特異的な領域として下前頭回三角部の活動が認められた。この領域は運動性言語野であるブローカ野の一部であり，IAPS の不快画像を用いた過去の研究では左扁桃体の活動と正の相関を示す部位として報告されている(Hariri et al., 2003)。そしてその活動は，不快画像の言語的解釈といった認知的負荷に関連していると考察されている。すなわち，不快感情生起時におけるこの領域の活動は感情調節のより認知的プロセスに関連していると考えられるため，恐怖症など不安障害における感情の認知的調節機能を評価する際のひとつの関心領域となりうる。

また、痛み動画の課題においては、痛み動画からコントロール動画の条件の脳活動の差分をとると、下部・中部側頭葉から下部頭頂葉にかけて、および下部前頭葉の領域とともに、体性感覚領域、及び視床—中脳水道周辺、島皮質の活動が有意であったのが特徴的であった。従来の報告でも、痛み刺激を実際に与えずとも、痛みに直接関わるネットワークが活動を示すことが示されており、痛みに対する情動的な反応を司っていることが分かる(Moriguchi et.al., 2007)。注射恐怖などの場合も、痛み刺激がない状態での痛みネットワークが活動することが考えられ、今後の脳活動のコントロールトレーニングの領域として有望であることが示唆された。

E．結論

本年度は、ストレス関連疾患のうち、まず恐怖症（注射恐怖など）に対するストレス課題の作成と、それぞれの課題が描出する脳内ネットワークの同定作業を行い、辺縁系・傍辺縁系（扁桃体、前帯状回、前/後島皮質)、大脳基底核、中脳水道周辺、脳幹など、また特に注射動画の課題においては、前述領域に加えて体性感覚領域や視床、脳幹などの活動など、期待された脳内ネットワークが確認され、課題の妥当性が示された。また、リアルタイム fMRI に必要なフィードバック解析システムをプログラミングによって構築し、動作確認を行った。今後は、より多くの大学生ボランティアによる健常群(n=20)、及び恐怖症などのストレス関連疾患群についてもリクルートし、サンプル数を増やしていく。さらに、当初予定にあった MRI システムから脳画像情報を即時に読み取る MRI シークエンスについてもより精度の高い 3T-MRI 用のものを開発し、高磁場 3T-MRI にシステムを導入していく。

F．健康危険情報

なし

G．研究発表

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H．知的財産権の出願・登録状況
（予定を含む。）

1. 特許取得

なし

2. 実用新案登録

なし

3.その他　　なし

＜参考資料１　ストレス関連疾患に関わると思われる脳領域についての概説＞

恐怖症、PTSD、強迫性障害、パニック等に関しては、多くの fMRI 研究がある（Etkin and Wager 2007 参照）。

多くの不安障害にとって、情動指摘をトリガーするキューへの恐怖・回避傾向は一般的で、恐怖刺激に対する fear response は共通のコンポーネントであると考えられる。動物実験のモデルから考えれば、扁桃体の機能不全は共通のものであると予想される。実際に扁桃体の過活動は PTSD や社会不安障害、特有の対象への恐怖症、パニック障害、強迫性障害に共通に認められるが、個々の研究での統計検定力の不足や、課題デザインの不均一性、患者群の選択方法の不均一、イメージング方法の不均一、統計解析の方法の不均一など、時に結果が統一感の欠けたものになり、再現性があるものであるかどうかの研究も必要である。

特に PTSD においては、扁桃体の活動が低下している、あるいはコントロール群と変わらないとする報告も散見され、さらに、恐怖症でも多くの報告が扁桃体の過活動を示唆する中、コントロール群と変わらないとするもの、逆に低下しているとするものがある。パニック障害・強迫性障害に関しても、扁桃体の過活動はむしろ例外的で、いつも認められるものではない。このような不均一から、扁桃体は PTSD や恐怖症、パニック、強迫性障害などにおいて中心的な役割を果たしているわけではなく、ある何らかの特殊な恐怖状況において役割を果たしているとする議論もある。他の脳領域に関しても結論は出ておらず、特に動物モデルによる研究が進まない部位ほどそれが顕著である。

こうした不安障害群は、症状など多くの点で異なっている。PTSD では過覚醒・乖離、感情鈍麻、悪夢やフラッシュバックなどの再体験現象などが特徴である。これらの症状は、通常の恐怖条件付けなどを行った際には観察されないものである。つまり、PTSD では、一般的な不安障害とは、むしろ異なった情動処理の障害があることを示唆している。しかし、一般の不安障害と PTSD を同時に検討したものは少ない。

Etkin and Wager (2007) は、PET と fMRI 研究を対象にして、voxelwise のメタアナリシス手法を用いて、PTSD、社会不安障害、恐怖症の脳活動パターンの比較を行っている（Table 1）。

PTSD 群では、情動処理課題において、扁桃体、海馬傍回、島皮質、頭頂下部、中部帯状回、楔前部が活動が亢進していた。社会不安では、扁桃体、海馬傍回、紡錘回、淡蒼球、島皮質、前頭下部、上側頭回が活動が亢進し、さらに、恐怖症では扁桃体、紡錘回、黒質、島皮質、中部帯状回が活動していた。よって、扁桃

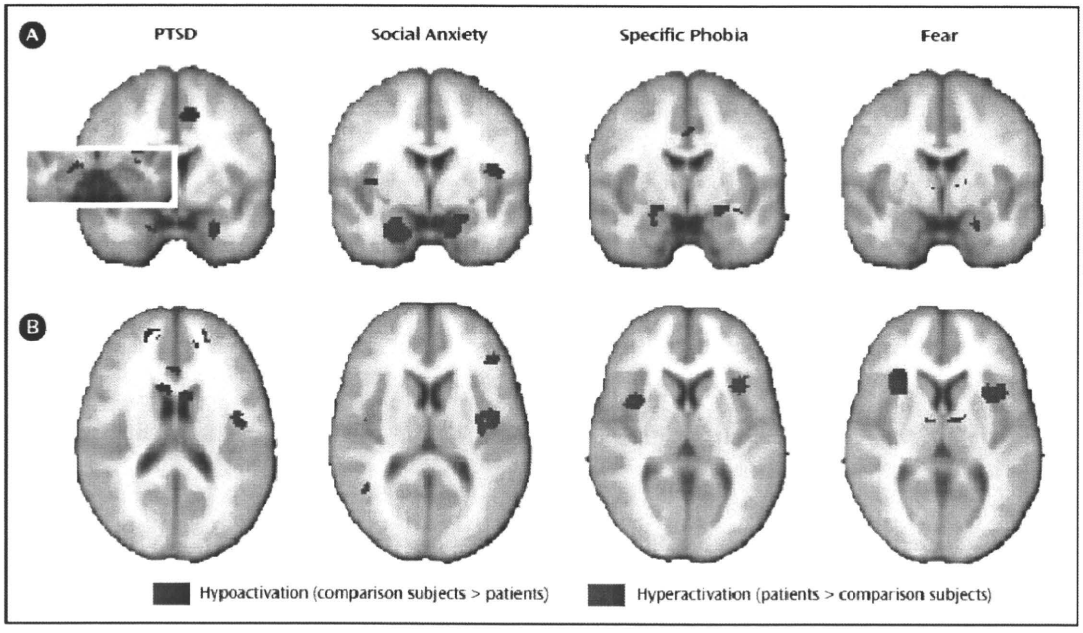
(Figure 1A) と島皮質 (Figure 1B) は全ての疾患に共通していた。また、この領域は、健常群での恐怖条件付けでも活動する領域であった。
PTSD においては、多くの領域で活動低下も見られる（Figure2A）が、特に重要なのは、5 つの研究が PTSD の症状の重症度と脳活動の相関をとっていて、全てが内側の前頭前野（mPFC）の活動低下が関連していることを示唆していた（Figure 2 参照)。

**TABLE 1. Summary of the Included Studies for the Meta-Analysis of Functional Neuroimaging Studies in PTSD, Social Anxiety Disorder, and Specific Phobia[a]**

| Disorder | Reference | Comparison Subjects | Patients | Emotional Stimulation | Included Contrasts | Symptom Provocation? | Method |
|---|---|---|---|---|---|---|---|
| Posttraumatic stress disorder (PTSD) | Bremner et al. (1999) (23) | 12 | 10 | Neutral and traumatic scripts | Trauma-neutral | Yes | Positron emission tomography (PET) |
| PTSD | Bremner et al. (1999) (24) | 10 | 10 | Neutral and traumatic sounds/pictures | Trauma-neutral | Yes | PET |
| PTSD | Bremner et al. (2004) (25) | 9 | 12 | Color naming color and emotional words | Emotional-neutral | No | PET |
| PTSD | Bremner et al. (2003) (26) | 11 | 10 | Neutral and emotional words | Deep emotional-neutral | No | PET |
| PTSD | Britton et al. (2005) (21) | 14 | 16 | Neutral and traumatic scripts | Trauma-neutral | Yes | PET |
| PTSD | Lanius et al. (2002) (27) | 10 | 7 | Traumatic script | Trauma-baseline | Yes | Functional magnetic resonance imaging (fMRI) |
| PTSD | Lanius et al. (2001) (28) | 9 | 9 | Traumatic script | Trauma-baseline | Yes | fMRI |
| PTSD | Lanius et al. (2003) (29) | 10 | 10 | Neutral and emotional scripts | Emotional-baseline for 1) traumatic, 2) sad, 3) anxious | Yes (only trauma) | fMRI |
| PTSD | Phan et al. (2006) (22) | 15 | 16 | Negative and neutral pictures | Negative-neutral (controls are combat) | No | PET |
| PTSD | Sakamoto et al. (2005) (30) | 16 | 16 | Masked traumatic and neutral images | Masked trauma-masked neutral | Yes | fMRI |
| PTSD | Shin et al. (1999) (31) | 8 | 8 | Neutral and traumatic scripts | Trauma-neutral | Yes | PET |
| PTSD | Shin et al. (2004) (6) | 19 | 17 | Neutral and traumatic scripts | Trauma-neutral for 1) male combat, 2) female nurse veterans | Yes | PET |
| PTSD | Shin et al. (2005) (7) | 13 | 13 | Fearful and happy faces | Fearful-happy | No | fMRI |
| PTSD | Williams et al. (2006) (8) | 13 | 13 | Fearful and neutral faces | Fearful-neutral | No | fMRI |
| PTSD | Yang et al. (2004) (32) | 6 | 5 | Neutral and traumatic images | Earthquake-neutral for 1) perception, 2) imagery | Yes | fMRI |
| Social anxiety disorder | Amir et al. (2005) (44) | 11 | 11 | Disgust and neutral faces | Disgust-neutral | Yes | fMRI |
| Social anxiety disorder | Kilts et al. (2006) (45) | 6 | 12 | Social anxiety and neutral imagery scripts | Social anxiety disorder-neutral script | Yes | PET |
| Social anxiety disorder | Lorberbaum et al. (2004) (9) | 6 | 8 | Speech anticipation | Anticipation-rest | Yes | fMRI |
| Social anxiety disorder | Phan et al. (2006) (10) | 10 | 10 | Harsh and happy faces | Harsh-happy | Yes | fMRI |
| Social anxiety disorder | Stein et al. (2002) (11) | 15 | 15 | Negative and happy faces | Negative-happy | Yes | fMRI |
| Social anxiety disorder | Straube et al. (2004) (12) | 10 | 10 | Angry and neutral faces | Angry-neutral for 1) implicit task, 2) explicit task | Yes | fMRI |
| Social anxiety disorder | Straube et al. (2005) (13) | 9 | 9 | Angry, happy, and neutral faces | Main effect for 1) angry, 2) happy, 3) neutral | Yes | fMRI |
| Social anxiety disorder | Tillfors et al. (2001) (14) | 6 | 18 | Public and private speaking | Public-private speaking | Yes | fMRI |
| Specific phobia | Dilger et al. (2003) (15) | 10 | 10 | Spider pictures | Spider pictures-baseline | Yes | fMRI |
| Specific phobia | Schienle et al. (2005) (16) | 13 | 10 | Phobia, fear, disgust, and neutral pictures | 1) Phobia-neutral, 2) fear-neutral, 3) disgust-neutral | Yes (only phobia) | fMRI |
| Specific phobia | Straube et al. (2006) (36) | 14 | 28 | Spider and control videos | Spider-control | Yes | fMRI |
| Specific phobia | Straube et al. (2004) (33) | 11 | 11 | Phobia and control words | Phobia-control | Yes | fMRI |
| Specific phobia | Straube et al. (2006) (17) | 12 | 11 | Spider and mushroom pictures | Spiders-mushrooms for 1) identification, 2) distraction tasks | Yes | fMRI |
| Specific phobia | Veltman et al. (2004) (18) | 6 | 12 | Spider and butterfly pictures | Spiders-butterflies | Yes | PET |
| Specific phobia | Wright et al. (2003) (34) | 10 | 10 | Fearful, neutral, and happy faces | Fearful-neutral | No | fMRI |

[a] Sample sizes, emotional stimulation paradigm used, included comparisons, and whether the study was a symptom-provocation study are noted. Overall, we analyzed data from 19 comparisons (see Methods) in PTSD, 11 in social anxiety disorder, and 10 in specific phobia, which together involved 172 patients with PTSD, 93 with social anxiety disorder, and 92 with specific phobia and 314 comparison subjects (175 for PTSD, 73 for social anxiety disorder, and 76 for specific phobia). Reference numbers are in parentheses. The sample size-weighted average age of the patient and comparison cohorts in the PTSD studies (mean=42.3, SD=17.5) was not significantly different from that in the social anxiety disorder studies (mean=30.4, SD=11.8; $p=0.10$ by t test). The PTSD cohorts, however, were older than the specific phobia cohorts (mean=24.7, SD=2.4; $p=0.001$), which did not significantly differ from the social anxiety disorder cohorts ($p=0.27$). The proportion of female subjects in the PTSD studies (50.3%) did not differ from the proportion in the social anxiety disorder studies (54.2%), which were both significantly different from the specific phobia studies, which were made up predominantly of women (93.5%; both $p<0.0001$ by chi-square tests).

Figure 1




[a] Results are shown for the amygdalae (A) and insular cortices (B). Note that within the left amygdala there were two distinct clusters for PTSD, a ventral anterior hyperactivation cluster and a dorsal posterior hypoactivation cluster. The right side of the image corresponds to the right side of the brain.

Figure 2

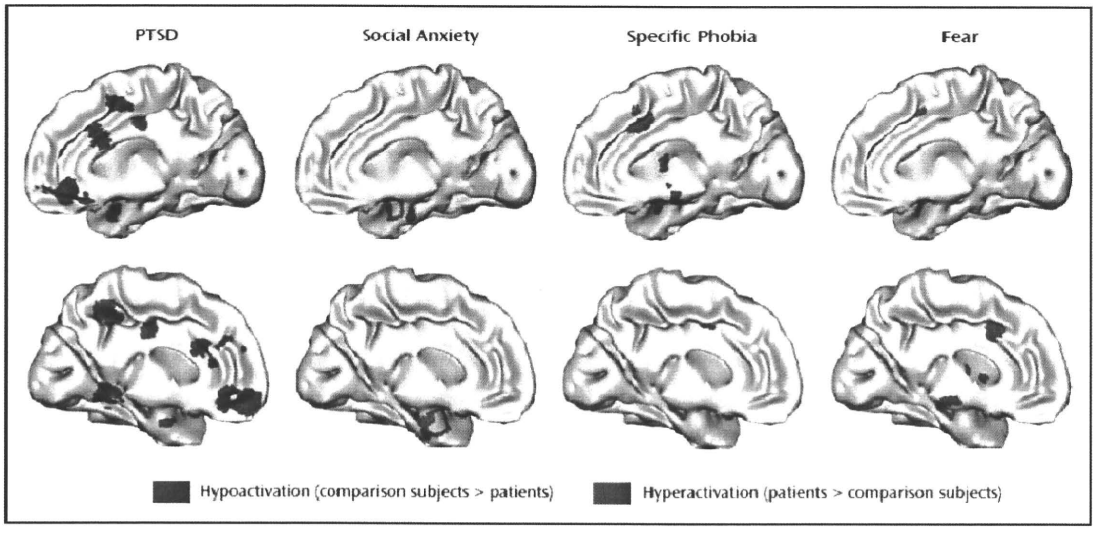
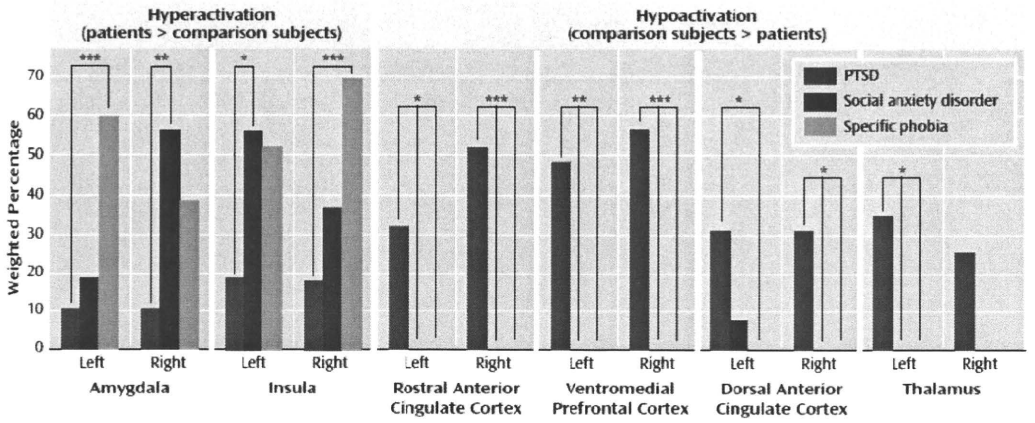


Figure 3




[a] (Left) Hyperactivation in patients, relative to comparison subjects, was observed more frequently in the amygdala and insula of patients with either social anxiety disorder or specific phobia than in patients with PTSD. (Right) Hypoactivation in the ventromedial prefrontal cortex, rostral and dorsal anterior cingulate cortices, and thalamus was specifically observed in patients with PTSD in relation to matched comparison subjects and not in patients with social anxiety disorder or specific phobia.
*p<0.05. **p<0.01. ***p<0.005.

＜参考資料２　本研究のプロトコール詳細＞

Clinical application of neurofeedback: real time functional magnetic resonance imaging (rtfMRI) study of psychiatric patients with stress-related disorders.

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<Summary>

Real time fMRI (rtfMRI) is recently spotlighted and is getting widely used to control our own brain activity. Emotional regulation with this technique, or clinical application to psychiatric disorders for instance, has been scarcely tackled, however. The aim of the study is to establish a training method of emotion regulation based on neurofeedback with real time fMRI (rtfMRI) targeting emotional brain regions, and seek the clinical application of this technique to stress-related disorders. Healthy volunteers and those with stress-related disorders including phobia, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD) will be recruited, and scanned using fMRI during observation of subject-specific visual stress task to localize subject-specific responsible regions beforehand. In subsequent rtfMRI training sessions, each volume EPI should be constructed immediately after each scanning and consecutively sent to a remote server or PC to process the data and calculate parameter estimates in the brain region online using in-house FASTR software. Hemodynamic response to the same emotional stimuli in the individually-localized target affective region is immediately fed-back in some visible manner to the participant online, and the participant try to reduce the stress-related neural activation through five training sessions. To confirm the regulatory effect of rtfMRI, we have the participants rate their subjective impacts of the emotional task before and after the sessions.
This study is done in National Institute of Mental Health, National Center of Neurology and Psychiatry (Tokyo, Japan), in collaboration with Martinos Imaging Center at the McGovern Institute, MIT, and Siemens Co, Japan.

## Introduction

Recent advance of neuroimaging technology including functional magnetic resonance imaging (fMRI) has enabled us to probe functional neural pathology in the psychiatric patients, and numerous fMRI studies have been done. Despite accumulating knowledge from these studies about psychiatric disorders, however, clinical application of these knowledge, especially for therapy to the patients, has not been scarcely tackled or explored. Neuroscience has not been a true benefit to these suffering patients so far.

Biofeedback is an effective therapeutic strategy which has been used widely for psychiatric and psychosomatic patients. The biofeedback provides the subjects immediate visible information of their inner physiological states which is not easily perceivable (e.g., using electromyogram, electroencephalogram, skin conductance, skin temperature), and makes the subjects easily access the inner physical and mental states. This process facilitates their control of bodily and mind states through trying to regulate the simultaneously obtained signals from their body. A recently developed 'neurofeedback' training with real time fMRI (rtfMRI) is based on an innovative idea that the direct neural activation measured by fMRI can be used as immediate feedback information (see [1, 2]). A neural activation (hemodynamic response) in a certain brain region is measured by fMRI, and this activation level is presented to the subject in the scanner at the moment (although the hemodynamic response delays for several seconds from the actual neural response). The subjects try to "control" the level of the activation in the brain region through training sessions. This new neurofeedback method began to be applied recently to the patient population (e.g., chronic pain patients [3]), and is expected to be a promising clinical approach also to the patients with psychiatric disorders like stress-related disorders.

Stress-related disorders (ICD-10, F4; neurotic, stress-related and somatoform disorders) are the mainstream in psychiatric clinical field, and rapidly increasing in number. Drug therapy alone is not effective in many cases, and the symptoms are frequently prolonged. Thus nonpharmacologic approaches to these patients should be explored. Real time fMRI should be a candidate for an alternative approach to the drug-resistant patients, or an enhancer which produces a synergistic effect on any psychotropic drugs.

A number of neuroimaging studies of stress-related disorders have emphasized altered affective processing in limbic and the adjacent brain regions. One good reason for application of rtfMRI to stress-related disorders is the location of the target limbic system and adjacent affective regions (e.g., amygdala, insula, anterior cingulate, orbitofrontal cortex, hippocampus, fusiform, thalamus, midbrain and brain stem). Other imaging strategies like near-infrared spectroscopy, electroencephalogram, or magnetoencephalogram are easy-to-use and good for detecting the signal from the surface of the brain, but can not detect such deep brain structures like affective limbic system. Positron emission tomography (PET) is not usable because of its low time resolution and does not fit real-time feedback. For now, rtfMRI is the only neuroimaging feedback technique to focus on affective neural networks which play central role for such psychiatric patients. A couple of rtfMRI studies appeared to show the possible emotional regulation with this technique [4-7], but there has been no

reports of successful emotional regulation with any clinical sample.

The purpose of the present study is to introduce the rtfMRI system to real clinical settings (Department of Radiology, Clinical Brain Imaging Center, National Center of Neurology and Psychiatry, Tokyo). Target clinical population is those with stress-related disorders including phobia, obsessive-compulsive disorder, and post-traumatic disorders. We develop the training system for such patients to control their own affective neural network in response to the stressors specific to each individual. We expect that the patients will get resistant to the affective stressors and control their own symptoms (i.e., inappropriate oversensitive responses to triggers). We never know any reports about clinical application of rtfMRI, focusing on their control of the affective brain circuitry. Also it will be a valuable trial where neuroscience will benefit patients in real therapeutic settings.

Method

*Participants*

We recruit right-handed healthy college student volunteers (n=20, age range 20-45) from colleges in greater Tokyo area as healthy control group. We also recruit right-handed patients with stress-related disorders (n=40, age range 20-45) from psychiatry outpatient clinic of the National Center Hospital in the National Center of Neurology and Psychiatry (Tokyo, Japan). The healthy and patient group are matched on age and sex. Among stress-related disorders (ICD-10, F40-F48; neurotic, stress-related and somatoform disorders), we focus three categories; 1) specific (isolated) phobias (ICD-10, F402, n=15), 2) obsessive-compulsive disorder (OCD; ICD-10, F42, n=15), and 3) post-traumatic stress disorder (PTSD; ICD-10, F43.1, n=10). Specific phobias include acrophobia (fear of heights), aichmophobia (fear of needles or of pointed objects), dentophobia (fear of dentists and dental procedures), zoophobia (fear of animals; dogs, bees, spiders, insects, snakes, birds). The reason for selecting these categories is that the triggers to initiate such patients' oversensitive response are concrete and easily specified, and we can identify the source of individual patient's problem and can make individually-specific stimulation for rtfMRI training. The study of such patients will be a milestone for the future studies of rtfMRI application to broader range of psychiatric disorders.

The study is approved by the local ethical committee, and all participants provide written informed consent, and are paid for their participation. This study is funded by Comprehensive Research on Disability Health and Welfare, Health and Labour Sciences Research Grants, Ministry of Health, Labour and Welfare (2010-2013).

*Psychological Measurements*

To assess the psychological property of each participant, the following questionnaires and structured interviews are used before the scanning.

*State-Trait Anxiety Inventory (STAI)* for measuring anxiety

*Beck Depression Inventory (BDI)* to exclude those with depression.

*Profile of Mood States (POMS)* for assessing transient, fluctuating active mood states at the moment.

*National Adult Reading Test (NART; Japanese version JART)* to estimate levels of

intelligence which moderately correlates the IQ.
*Edinburgh Handedness Inventory* to ensure the participant's right-handedness.
*Yale Brown Obsessive Compulsive Scale (Y-BOCS)* if the participant is considered as suffering obsessive compulsive disorder (OCD).
*Impact of Event Scale (IES-R)* to assess clinical symptoms due to a traumatic event if the participant is diagnosed posttraumatic stress disorder (PTSD).
*Mini-International Neuropsychiatric Interview (M.I.N.I.)* to assess clinically psychiatric disorders, including not only stress-related disorders but also other psychiatric problems such as mood disorders, psychosis, anxiety disorders, addiction, eating disorder, and antisocial personality.

*Visual Stimuli*
We create picture and/or movie stimuli illustrating individually different triggers (e.g., pictures of needle, movies of climbing up the ladder). For ethical reasons, the intensities of these emotional stimuli (i.e., subjective impact to each participant) should be controlled so that the participants can bear the stimuli, as well as experience some difficulty and feel stressed. So the participants were interviewed well before the stimuli are created.
For example, a participant with acrophobia (fear of heights) will be shown the pictures or movies depicting some situations of the heights, but the intensity of the stimuli will not be maximum but limited as the participants can experience them with bearable stress. Once the preliminary stimuli are created, they will be presented to the participants (on a PC) and the intensities are rated by them with visual analogue scale (VAS). The participants will be asked about if they can bear the stimuli in the scanner, and the stimuli are selected based on each participant's agreement. Also, we create neutrally-valenced control pictures (or movies) which match the task pictures with regard to picture size, color, contrast, and luminance.

*Functional localizer scanning*
To localize brain regions individually associated with the subject-specific affective stimuli beforehand, a localizing fMRI scanning is conducted for each participant. The visual stimuli are presented with a block design fashion; one block consists of six static stimulus pictures (or two movies), with each picture presented for 5 seconds (or with each movie presented for 15 seconds). One fMRI run (session) consists of ten task and ten control blocks and, in the first and last period of the run, additional two 30-second baseline blocks with fixation cross are presented, resulting in a 11-minute run in total.
For image acquisition we use a Siemens Magnetom Vision-Symphony 1.5T whole body high-speed imaging device equipped for echo planar imaging (EPI) (Siemens Medical Systems, Erlangen, Germany) with an 8-channel gradient head coil. Expandable foam cushions restrict head movement. After a scout image is acquired and shimming procedures are performed to optimize field homogeneity, structural MR images are acquired with a magnetization-prepared rapid gradient echo sequence (MPRAGE; TE/TR, 4.4/11.4 ms; flip angle, 15 degree; acquisition matrix, 256 × 256; 1 NEX FOV, 31.5 cm; slice thickness, 1.23 mm). Changes in blood oxygenation level-dependent T2*-weighted magnetic resonance (MR) signal [8, 9] are measured using a gradient echo-planar imaging (EPI) sequence (repetition time [TR] = 2500 ms, echo time [TE] = 40 ms, field of view [FOV] = 220 mm, flip angle = 90 degree, 64 × 64 matrix, 40 slices

per slab, slice thickness 3.0 mm, 0.3 mm gap, voxel size = 3.44 × 3.44 × 3.3 mm). A total of 269 EPI volume of whole brain images are acquired along the AC-PC plane during visual stimulation presentation. The first five scans are discarded because of instability of magnetization; therefore, we obtain 264 volumes of EPI for analysis. The stimuli are projected onto a screen ~50 cm from the participant's head. The participants view the screen through a mirror attached to the head coil.

Image processing is carried out using statistical parametric mapping software (SPM8, Wellcome Department of Imaging Neuroscience, London, UK). The EPI images are realigned and co-registered to the participants' T1-weighted MR images. Then, the T1 images are transformed to the anatomical space of a template brain whose space is based on the MNI (Montreal Neurological Institute) stereotactic space. The parameters for the transformation are applied to the co-registered EPI images. The normalized images are smoothed by a 6-mm FWHM Gaussian kernel. A subject-wise analysis is done using the general linear model with the hemodynamic response function modeled as a boxcar function whose length cover each task or control block. To test the hypotheses about regionally specific effects in the task condition compared to control condition, the parameter estimates of task and control conditions are compared by means of linear contrasts for each epoch (affective task versus control condition). The resulting set of voxel values for the task vs control contrast constitutes a statistical parametric map of the t statistic SPM(t).

We have a hypothesis that some emotion-related regions play an important role to exaggerate the affective response to stimuli, so we focus the brain areas which have been consistently reported in previous neuroimaging studies about emotion [10-20]. We focus 1) amygdala (AMG), 2) hippocampus (HC), 3) parahippocampus (pHC), 4) fusiform gyrus (FG), 5) anterior/posterior insula (AIC/PIC), 6) inferior frontal gyrus (IFG) or ventrolateral prefrontal cortex (VLPFC), 7) orbitofrontal gyrus (OFG), 8) medial prefrontal cortex (MPFC), 9) dorsolateral prefrontal cortex (DLPFC), 10) pons, 11) midbrain (Mb), 12) thalamus (Th), 13) striatum (St), and 14) anterior/posterior cingulate cortex (ACC/PCC). First, the most remarkably activated cluster (from task vs control contrast) is picked up among these affective areas defined by Automated Anatomical Labeling atlas database (AAL atlas) [21] implemented in WFU-Pickatlas software [22, 23]. A sphere region of interest (ROI) (5-10mm in radius) is set centered at the peak coordinate as the target region.

*Neurofeedback (rtfMRI)*

The participants are instructed to downregulate their target region activity for block periods of 30 sec ("down") which follows preceding baseline periods of 30 s ("rest") (i.e., 10 down-rest repetitions per run). One training run lasts for 11 min. They undergo five neurofeedback runs, yielding an overall training time around 1hr per participant. Imaging parameters are the same as that described in the localizer section above.

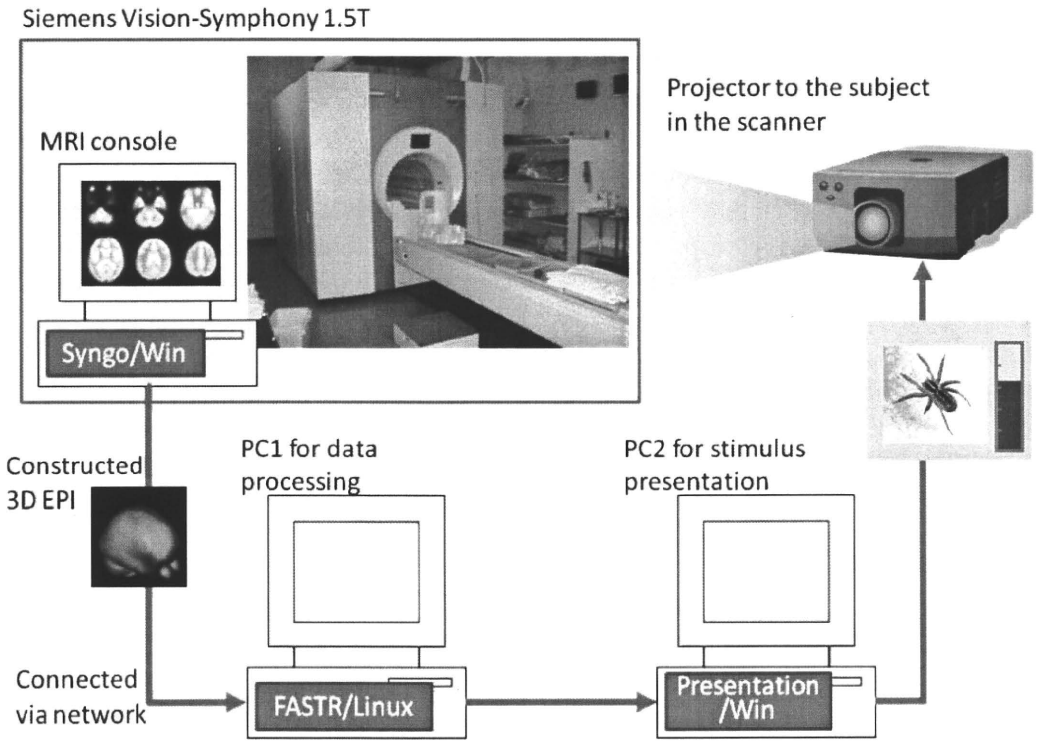
We suggest to the participants that meta-cognitive 'mindfulness'-like approach, which have been argued as an efficient way of emotional regulation [24-27], may be employed and give some brief lecture about mindfulness approach. But we do not force a specific strategy, and suggest instead that participants should monitor the feedback signal and 'tune' their strategy during successive blocks to look for the most efficient approach.

For the continuous feedback provided in our study, a picture of a thermometer whose temperature reflects amplitude increases of the fMRI signal in the target area, relative to

a baseline period, is presented beside an affective scene. The thermometer was updated every 2.5 s to inform participants about their performance.

*Online data analysis of rtfMRI*

Online ('real time') fMRI is made possible via a fast connection between the MRI scanner and the analysis computer (see Figure below). After acquisition and reconstruction at the scanner computer, data from the scanner is sent to the analysis computer. An in-house real time fMRI software (FASTR) detects, imports and analyzes the data, corrects them for angular and translational motion and added them to an incremental general linear model calculation. The signal estimate for each incoming functional imaging volume within the selected region-of-interest was fed-back to the participant, from a projector, with the in-built thermometer display. Delay time between the image collection and presentation of the feedback signal to the participant was less than 100 ms.




*Offline data analysis of rtfMRI*

Raw EPI data obtained from rtfMRI sessions are further pre-processed offline and analyzed with SPM8 as the localizer fMRI data have been analyzed. The signal change in the target region compared to rest period are calculated using GLM in each rtfMRI session, and we see if the parameter estimates across five training rtfMRI sessions will be gradually and successfully reduced as the sessions proceed.

*Subjective measurement of emotional stimuli*

We use a 10-point visual analogue scale (VAS) to have the participants rate the

subjective impact of all the stimuli used in the sessions before and after rtfMRI sessions, to see if the entire training is successful to reduce the subjective impact of the stressful stimulus on them.

*Sham rtfMRI training sessions*

It is highly supposed that only repetitive presentation of the emotional stimuli is effective to desensitize the participant in response to the stimuli because 'exposure therapy' has been regarded and frequently used as an efficient therapeutic strategy in real clinical settings [28-33]. Also, the participants' trial itself (i.e., to struggle to reduce the emotional impact in any way), regardless of the correctness of the feedback information, is suspected to have some effects to alter the participant's sensitivity to the emotional stimuli. To confirm the therapeutic effect specific to the neurofeedback, 'sham' training sessions are conducted to a part of the healthy volunteer participants (n=10). They undergo sham rtfMRI sessions before real rtfMRI sessions without notice of if the sessions are real or sham. Only difference between real and sham sessions is that neurofeedback information is reversed in sham sessions; the more activation in the target region shows, the less amplitude the thermometer indicates. At the initial time when the task blocks start, the meter indicates relatively high amplitude of activation, and the meter never grows and only goes downward when the activation increases (i.e., if the activation actually decreased, the meter does not response anymore and stay still). In this way, the participants are engaged in making efforts to, in their mind at least, "reduce" the activation (i.e., their attitude to the training is the same as that to the real sessions), and feedback information is seemingly true to them, but is not actually correct.

*Familiarization rtfMRI session*

To have the participants be familiarized with the general procedure of rtfMRI and experience the time-lag between the stimulus (or relevant neural activation) and feedback information, we do a familiarization rtfMRI session before the all rtfMRI training sessions. A localizer fMRI (to localize individual visual area) is conducted in an event-related fashion with the same EPI scanning parameters as other fMRI/rtfMRI sessions. The run consists of 30 events (7.5-min run), and in each event, alternating white/black 4Hz checkerboard stimulation appears for 2.5 seconds with 12.5 seconds of interstimulus interval. After usual preprocessing and GLM analysis with SPM8 to calculate the parameter estimate on event-related hemodynamic response, the most highest activation peak is picked up and sphere ROI is set centered at this peak in the primary visual cortex. In a familiarizing rtfMRI run, instead of the presentation of the emotional stimuli during the task blocks, they undergo the same checkerboard visual stimulation during 30-second task block following 30-second baseline. Alternating white/black 4Hz checkerboard appears for 2.5 seconds with 12.5 seconds of interstimulus interval (i.e., two times in a task block). In this manner the participants learn the relationship (delay) between actual perception of stimuli (or mental activity) and fed-back information based on the delayed hemodynamic response.

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