神経伝達を終了させる．このモノアミントランスポーターは，細胞膜に存在する細胞膜モノアミントランスポーターと，シナプス小胞に存在するシナプス小胞モノアミントランスポーターの２種類が知られている．モノアミン受容体は多数のサブタイプが存在するのに対し，細胞膜モノアミントランスポーターは各モノアミンに一種類しかなく，さらにシナプス小胞モノアミントランスポーターはすべてのモノアミンを基質としている．このことから，モノアミントランスポーターはモノアミン神経伝達の制御には極めて重要な役割を果たすと考えられる．

細胞膜モノアミントランスポーター

細胞膜モノアミントランスポーターは，神経終末の細胞膜に存在し Na^+/Cl^- 依存性にモノアミンを神経終末内に取り込む膜蛋白質であり，アミノ酸トランスポーターなどとともに大きな遺伝子ファミリーを形成している．細胞膜を 12 回貫通し，N，C 末端はともに細胞内に存在する構造をとっている．神経終末から放出されたドーパミン(DA)，ノルエピネフリン(NE)，セロトニン（5-HT）は細胞膜モノアミントランスポーターにより素早く神経終末に再取り込みされ，神経伝達は終了させられる．細胞膜モノアミントランスポーターはモノアミンそれぞれの作動性ニューロンの主に前シナプス神経終末の細胞膜に位置し，DA，NE，5-HT それぞれの基質に対応して三種類に分かれ，DA トランスポーターは DA 作動性ニューロンの，NE，5-HT はそれぞれの作動性ニューロンの主に前シナプス神経終末の細胞膜に位置している（曽良，2000）．

DA，NE，5-HT トランスポーターは抗うつ剤や覚醒剤の標的分子である．ドーパミントランスポーター（DAT）はコカイン，アンフェタミン，メチルフェニデート等の覚醒剤の標的分子，あるいは MPP+，6-OHDA 等の神経毒の侵入経路として長らく研究されてきた．アミノ酸トランスポーターは神経細胞にもグリアにも見出されるが，DAT は DA 神経にのみ存在するため，DA 神経の最も良い指標となる．ノルノルエピネフリントランスポーター(NET)，セロトニントランスポーター（5-HTT）は抗うつ剤の標的分子であることから，躁うつ病，不安などの病態に関与していると考えられている．

シナプス小胞膜モノアミントランスポーター（VMAT）

一方，シナプス小胞モノアミントランスポーター（VMAT）は，DA，NE，5-HT，ヒスタミンすべてを基質とする単一の蛋白であり，神経終末内のシナプス小胞膜に存在する．このシナプス小胞モノアミントランスポーターは細胞質で合成されたモノアミンを H^+ 依存性にシナプス小胞に貯蔵し，シナプス間隙へのモノアミン放出に備える．VMAT 1 は主に副腎に発現し，VMAT 2 は主に中枢神経系に発現している．アンフェタミンは VMAT を介してシナプス小胞に貯蔵されているアミンを細胞質に排出させ，そのアミンを細胞膜の DAT を通じてシナプス間隙に放出させる．レセルピンは VMAT に結合しシナプス小胞のアミン輸送を阻害する．

2. 報酬系高次神経機能（覚醒剤の標的分子）

コカインやアンフェタミンなどは依存性薬物である覚醒剤としてモノアミントランスポーターに作用する．そのためモノアミントランスポーターは古くから依存性薬物の標的分子として，これまで薬理学的な解析が詳細に行われてきた（図 1）．依存性薬物の共通作用部位として腹側被蓋野のドーパミン神経細胞から，辺縁系ことに側坐核や扁桃体に投射する神経回路が注目されるようになり，「ドーパミン仮説」が提唱されている．コカインは三種類のモノアミントランスポーターに親和性を持つが，報酬効果はドーパミントランスポーター（DAT）を介していると考えられ，「DAT 仮説」が提唱されている（Kuhar，1991）．依存性薬物によって引き起こされる薬物依存は，この報酬系高次神経機能の障害によると考えられ，多くの精神神経疾患に伴う情動障害を理解する上で有用なモデルと考えられる．

コカインはドーパミントランスポーター，セロトニントランスポーター，ノルエピネフリントランスポーターの何れにも作用することが明らかになってきたものの，その主たる作用部位あるいはモノアミン間に相互作用があるのかといった作用メカニズムについては依然不明である．我々は，モノアミントランスポーター欠損マウスを作製しコカインの作用を検討した．DAT 欠損マウスは，組織形態学的異常は認められないものの，発育は遅延している．興味深いことに野生型にくらべて 3～6 倍の極めて活発な運動量を示し，DA 再取

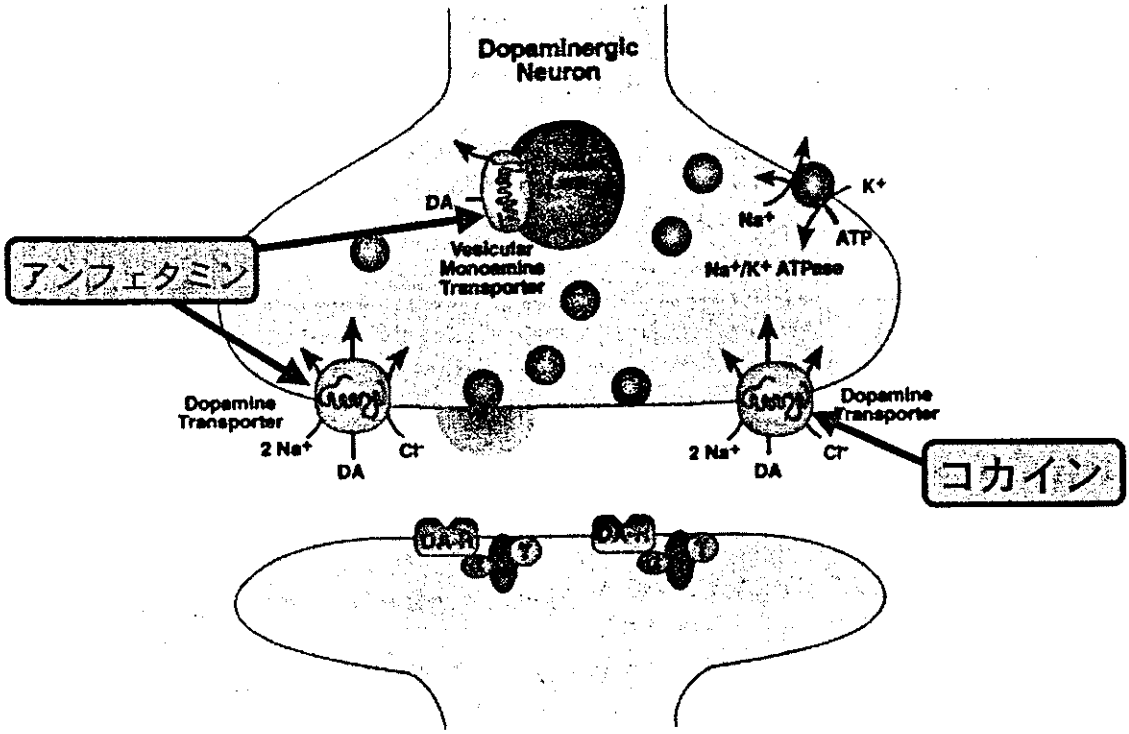

図1　覚醒剤の標的分子
ドーパミントランスポーター（DAT）などの細胞膜モノアミントランスポーターは，Na^+/K^+-ATPaseにより作られたNa^+勾配を利用して，細胞外に放出されたモノアミンを再取り込みする．シナプス小胞モノアミントランスポーター（VMAT）は，H^+と共役して細胞質中のドーパミンなどのモノアミンをシナプス小胞内に貯蔵し，放出に備える．ドーパミン神経では，コカインはDATに作用する．アンフェタミンはDATのみならず，VMATにも作用する．(Amara SG，1998より改変引用)

り込みの欠損はDA合成酵素，DA受容体のダウンレギュレーションにおいても代償できなかったことを示している(図2)．また，5-HTT，NET数の代償性変化は見られなかった．しかし，コカイン，アンフェタミンの投与により野生型マウスで見られる運動量の増加作用は，DAT欠損マウスにおいては消失していることから，覚醒剤の運動量増加作用にはDATが不可欠であることが示唆される(Sora，1998)．一方，コカインの報酬は三種類のモノアミントランスポーターの中でもDATを介しているというDAT仮説が想定されてきたが，DAT欠損マウスにおいてコカインの報酬が保たれていたことから，DAT仮説の見直しが行われている（Sora，1998；Rocha，1998)．

他のモノアミントランスポーター欠損におけるコカイン報酬については，5-HTT，NETが欠損するとコカイン報酬は減少するどころかむしろ増加する結果が得られた(Sora，1998；Xu，1999)．これらのことから，コカインの報酬は，DAT，5-HTT，NETがそれぞれ単独に欠損しても他が代償して保持されることが考えられる．そこで次にダブルノックアウトマウスを作製して検討した．コカインの報酬はDATが完全欠損し，5-HTTが完全欠損あるいは部分欠損している遺伝型マウスでは消失した．しかし，5-HTTが完全欠損していてもDATが部分欠損の場合では保持された（Sora，2001)．これらの結果により，コカイン報酬にはDATと5-HTTが共に関与し，5-HTTよりもDATがより重要な役割を果たしていると考えられた．「DAT仮説」は最初に提唱された以上に複雑な系と思われる(Kirkpatrick，2001；Uhl，2002)．*In vitro*の結合実験において，モノアミンのトランスポーターへの結合親

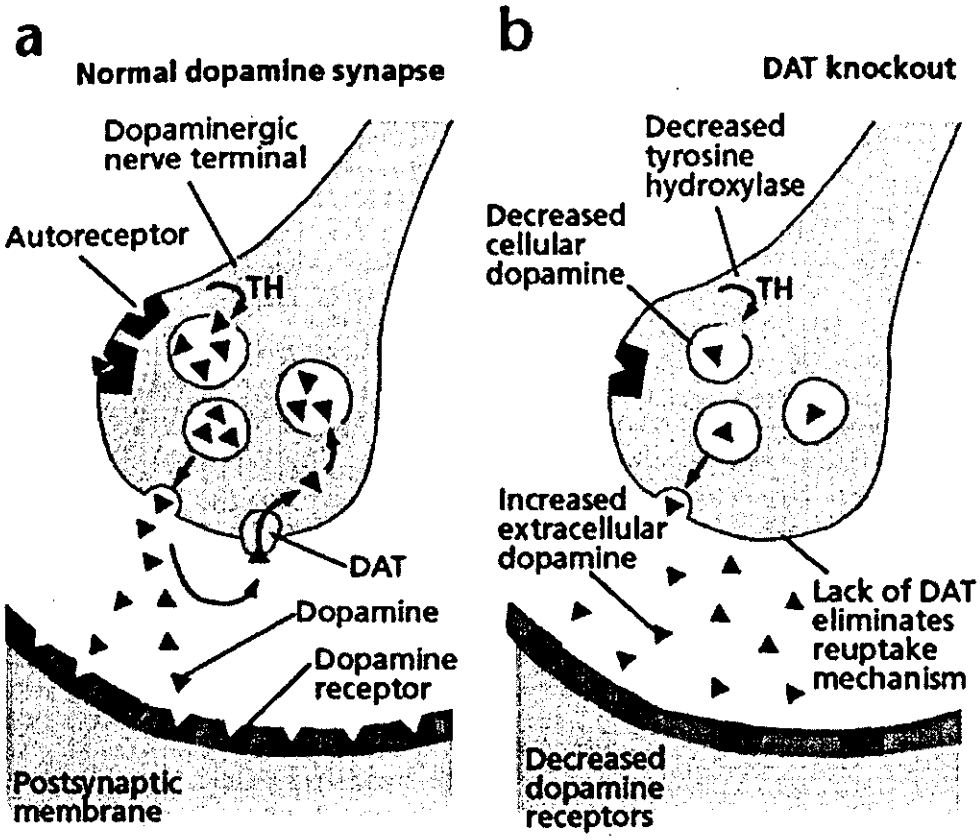

図2 ドーパミントランスポーター（DAT）欠損マウス
野生型マウスではドーパミン神経終末から放出されたドーパミンは速やかにDATにより再取り込みされる．これに対し，DAT欠損マウスでは，DATが神経終末に発現していないためDATの再取り込みは見られない．このため細胞間隙はドーパミン過剰となりドーパミン合成の低下や受容体の発現レベルの低下が見られる．(Caine, 1998より改変引用)

和性は特異性が知られているものの，この点を含めて補完作用の可能性を今後検討していくことが重要である．

さて，アンフェタミンでは，慢性投与により逆に作用が増強するという逆耐性現象が知られている．VMAT2ヘテロノックアウトマウスにおいてアンフェタミン投与による運動量が野生型に比べて増加していたが，反復投与後は運動量のよりいっそうの増加は起こらず，逆耐性現象は観察されなかった．このことは覚醒剤の逆耐性現象にはVMAT遺伝子の正常な発現が必要であることを示唆している（Uhl, 2000）．

3. モノアミントランスポーターと抗うつ剤

三環系抗うつ剤はノルエピネフリンやセロトニンの取り込みを阻害することから，NET, 5-HTTは躁うつ病の病態に関与すると考えられている．躁うつ病患者の血小板での5-HTの取り込み能が減少していることから，5-HTTは躁うつ病の体質マーカーの一つと想定されている．5-HT関連遺伝子の中でも5-HTT遺伝子の発現調節を行うプロモーター領域の配列は短い遺伝子多型をもつ群と長い群に分かれることがわかり，5-HTT遺伝子が短い群では，より強い不安・抑うつ人格傾向を示すことが報告され，分子遺伝学的な解析も

注目を集めている．

5-HTTは選択的セロトニン取り込み阻害薬(SSRI)などの抗うつ薬，MDMA（エクスタシー）などの依存性薬物の作用部位である．抗うつ薬では近年，セロトニン・ノルエピネフリントランスポーター阻害薬(SNRI)と言われる，セロトニントランスポーターおよびノルエピネフリントランスポーター双方を阻害する薬剤が上市され一定の効果をあげている．

抗うつ剤のスクリーニングテストでは尾懸垂テスト(tail suspension test)が利用されている．これは，マウスを尾で固定して逆さに吊した時の活動性が抗うつ剤により賦活化されることを利用したものである．NET欠損マウスでは，この尾懸垂テストでの三環系抗うつ剤の効果が減弱していることが報告された（Xu, 2000）．抗うつ剤の作用部位としてNETが重要であることを強く支持している．さて，近年抗うつ剤投与により前頭前野皮質の細胞外ドーパミン濃度が上昇するという報告(Tanda, 1996)がありこれまで考えられてきた以上にモノアミン間の相互作用があるものと思われる．最近我々はDAT欠損マウスへの抗うつ剤投与によっても側坐核での細胞外ドーパミン濃度が上昇することを見出した（未発表）．今後DATあるいはDAの関与の見直しも必要と思われる．

今後，NET欠損マウスを含めたモノアミントランスポーターのダブルKOマウスを用いることにより，モノアミンおよびモノアミントランスポーター間の相互作用の解明が期待される．

4. まとめ

精神神経疾患の「作業仮説」，覚醒剤や抗うつ薬などの向精神薬の作用機序を検証する上で，モノアミントランスポーター遺伝子ノックアウトマウスは高次神経機能の解明あるいは精神神経疾患の動物モデルとして有用であることを示した．さらに，対応するモノアミン以外の他のモノアミントランスポーターによる補完作用が，覚醒剤，抗うつ剤の新たな作用メカニズムである可能性が示唆された．ノックアウトマウスを利用することにより，従来の阻害剤では分からなかった新たな知見が今後，得られてくるものと期待される．

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Abstract

Catecholamine and higher neuronal function

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Monoaminergic nervous system exerts in higher neuronal regulations such as motor function and reward, suggesting that monoamines are involved in the pathology of many neuropsychiatric diseases. Monoamine transporters exist in both plasma membrane and synaptic vesicle membrane. Plasma membrane transporter is a target for antidepressants and addictive drugs. Only single monoamine transporter is expressed on the corresponding monoaminergic neuron, while there are many subtypes for monoamine receptors. However, synaptic vesicular transporter uptakes every monoamine as a substrate. These suggest the importance of monoamine transporter for the regulation of monoaminergic neurotransmission. Animal model is an important tool to understand pathophysiologies of many illnesses and to develop the therapies. We have generated monoamine transporter knockout mice as models for neuropsychiatric disorders. In this paper, we will review the function of monoamine transporters and introduce usefulness of the knockout mice as animal models to study higher neuronal functions and mental illness.

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特集2：生物学的精神医学研究の現状と展望（3）

311-316

遺伝子改変マウスモデルを用いた薬物依存と統合失調症の病態研究
——東北大学精神・神経生物学分野における取り組みを中心に——

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Key words：transgenic mice, monoamine transporter, monoamine receptor, drug abuse, schizophrenia

1．はじめに

東北大学精神・神経生物学分野は精神神経学分野に加えて精神医学教室の流れを汲む教室として精神疾患の生物学的研究を行うために平成14年春に新しく開講された。当教室では，主に筆者らが作製したモノアミン神経伝達に関与する遺伝子ノックアウトマウス（以下KOマウス）を用いて，薬物依存と統合失調症の病態研究を行っているので紹介したい。

精神疾患の動物モデルは，身体疾患同様に複雑な臨床症状を解析可能とするために病態解明，治療法の開発に欠かすことができない。もちろん，精神疾患においてヒトと動物の種族差は身体疾患以上に大きく，精神疾患の多彩な症状のあらゆる面を表現できる完璧な動物モデルは存在しない[33]。しかし，精神疾患の一群の症状，病態メカニズム，治療薬の反応性などが現在までにさまざまな動物モデルを用いて検討されてきた。このような動物モデルの中には遺伝モデルも開発されてきたが，多くは突然変異体あるいは人為交配の経過の途上で発見されたために，関心のある遺伝子の変異モデルを得られることは偶然に頼るしかなかった。近年，標的分子の遺伝子を狙って変異を導入する分子遺伝学的手法が開発され，遺伝子変異マウスが作製可能となった[26)29)]。遺伝子変異マウスのうちで遺伝子の発現を欠損させたノックアウトマウスが作成され，新しい疾患動物モデルとして数多くの研究が行われてきた[3)18)24)28)]。本稿では，薬物依存の病態の基礎となる報酬系のメカニズム，統合失調症と関連する逆耐性現象・プレパルスインヒビションを中心に当教室で行われている研究を紹介する。

Pathophysiology of drug addiction and schizophrenia : research using transgenic animal models at Department of Psychobiology, Tohoku University Graduate School of Medicine

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2．薬物依存と報酬系

薬物依存形成の基礎となる報酬系の研究に動物モデルが用いられてきた。依存性薬物が標的分子にどのように作用するのかについて，これらの動物モデルを用いてさまざまなアプローチがなされてきたが，従来の薬理学的な手法では標的分子に特異的に結合する化合物を得ることは困難であった。しかし，生体内で標的分子の遺伝子に変異を起こさせる遺伝子改変動物モデルを用いることにより，従来の古典的な薬理学の手法では明らかにすることが難しかった知見が得られるようになった[31]。本稿では覚醒剤の標的分子であるモノアミントランスポーター[22]の欠損マウスを用いて得られた薬物依存と報酬系の分子メカニズムを紹介する。

コカインはモノアミントランスポーターに結合するが，報酬効果はそのうちのドーパミントランスポーター（DAT）を介していると考えられ，「DAT仮説」が提唱されていた[21)22)]。筆者らのグループはDATが欠損しているマウスを作製し，コカインによる運動量の増加は消失しているにもかかわらず，条件づけ場所嗜好性試験，静脈内自己投与によるコカインの報酬効果は保持されていることを見出した[27]。さらにセロトニントランスポーター（SERT）あるいはノルエピネフリントランスポーター（NET）-KOマウスにおいてもコカインの報酬は減少するどころか，むしろ増加する結果が得られた。これよりSERT，DAT，NETがそれぞれ単独に欠損しても，他のトランスポーターが補い，コカインの報酬が保持されることが推測された[34]。そこでDATとSERTが共に欠損するマウスモデルを作製し，コカインの報酬が保持あるいは消失するかどうかを検討したところ，DATの完全欠損にSERTの部分あるいは完全欠損が加わるとコカインの報酬は消失した[25]。一方，SERTが完全欠損してもDATの発現が部分的に存在するとコカインの報酬は保持された。このことから，コカイン報酬にはDATとSERTが共に関与しているが，SERTよりもDATがより重要な役割を果たしていると考えられ，「DAT仮説」は最初に提唱されたものとは異なり，複雑な系であることが明らかとなった[23)34)]。

そこで我々は，報酬に関する上記の結果に対応する脳内モノアミン神経伝達を解析することを目的に，脳内微少透析法を用いてコカインに対する線条体（CPu），側坐核（NAc）と前頭前野皮質（PFc）細胞外ドーパミン（DA*ex*），セロトニン（5-HT*ex*）濃度の変化を検討した。コカインの報酬に対応してDA*ex*が増加したのは，側坐核，前頭前野皮質ではなく，線条体であることがわかった[19]。DAT-KOマウスではDATが欠損しているにもかかわらずコカインの報酬があり，DAT/SERTダブルKOマウスで報酬がなくなるのは，線条体においてDAT-KOマウスでDA*ex*の増加があり，DAT/SERTダブルKOマウスではDA*ex*の増加がないからと考えられる。DAT-KOマウスでDATが欠損しているにも関わらずDA*ex*が増加しているのは，SERTがDA再取り込みを補完したことを示唆している。側坐核ではDATが欠損するとDA*ex*の増加が見られなかった。前頭前野皮質ではDAT-KOマウス，DAT/SERTダブルKOマウスでもDA*ex*の増加が見られ，前頭前野皮質ではNETによるDA再取り込みの補完が考えられた。5-HTについては，SERT-KOマウスで前頭前野皮質での5-HT*ex*の増加が見られないが，線条体，側坐核では増加が見られ，DAT/SERTダブルKOマウスで見られなくなったことから，線条体，側坐核ではDATが5-HTの再取り込みを補完していると考えられた。これらの結果は，コカイン報酬にはDATとSERTが共に関与し，同族トランスポーターの補完作用が存在することを示唆している。

3．統合失調症の発症脆弱性モデルとしての逆耐性現象

実験動物に覚醒剤やコカインのような中枢興奮薬を反復投与すると，移所運動量や常同行動が増加し，長期断薬後も同量またはそれ以下の薬物の再投与でこの増加が再現される[17]。この逆耐性現象はヒトの薬剤性精神病や統合失調症の症状再燃

に酷似することから，これらの精神病の有力な発症脆弱性モデルとされている[11)-13)]。統合失調症患者に覚醒剤を投与して線条体後シナプスドーパミンD2受容体の占拠率をSPECTで調べた米国のグループは，線条体DA神経終末からのDA放出量が正常人の約2倍に上昇していることを報告している[6)]。この知見は，統合失調症患者のDA神経系では逆耐性現象を形成した動物と同様の変化が生じていることを初めて示し（endogenous sensitization），統合失調症動物モデルとしての逆耐性の妥当性を示しているという点で意義深い。

当教室では主にモノアミントランスポーターKOマウスを用いて逆耐性現象の形成を検討している。DATはコカイン，メタンフェタミンの標的分子であり，DATが完全欠損したDAT-KOマウスはDA再取り込み機構が欠損しているためDA*ex*が正常の10倍に増加し，表現型として自発運動量の増加，新奇環境における馴化の低下を示す[21)27)]。コカイン，メタンフェタミンの移所運動量増加作用はDAT-KOマウスでは消失し，逆に鎮静効果が現れる[30)]。DATヘテロKOマウスでは，メタンフェタミン反復投与により逆耐性現象は形成されたが，発展は野生型に比して有意に抑制されていた。これらの結果より，中枢刺激薬の移所運動量増加作用にはDATが不可欠であること，逆耐性現象の正常な発展にはDATの完全な発現が必要であることが示唆された。脳内微少透析法による検討では，DATヘテロKOマウスにおいてメタンフェタミン投与時線条体でのDA放出は野生型に比して減少していた。移所運動の逆耐性形成には腹側被蓋野から側坐核へのDA伝達が重要であると考えられているが，この結果からは逆耐性発展における線条体DA伝達の関与が示唆された。

シナプス小胞トランスポーター2（VMAT2）はモノアミン小胞上に存在し，モノアミンを小胞内に汲み上げ貯蔵する。メタンフェタミンはVMAT2を介してシナプス小胞に貯蔵されているモノアミンを細胞質に排出させ，そのモノアミンを細胞膜上のトランスポーターを介して逆流出させる[35)]。VMAT2完全欠損マウスは致死性であるため，ヘテロKOマウスでの検討を行った。VMAT2ヘテロKOマウスのメタンフェタミン，コカイン投与による急性運動増加作用は野生型に比べて増加しているが，条件付け場所嗜好性試験における覚醒剤の報酬効果は減少しており，メタンフェタミン反復投与での逆耐性現象も形成されなかった[21)32)]。この結果はメタンフェタミンが細胞膜とシナプス小胞トランスポーターの両者を標的とすることに起因している可能性があり，メタンフェタミンの逆耐性現象形成にはVMAT2遺伝子の正常な発現が必要であることが示唆された。中枢刺激薬はSERT，NETにも比較的高い親和性で結合する。SERT-KOマウスの5-HT*ex*は野生型の10倍を示す。SERT-KOマウスにおけるメタンフェタミンの移所運動量増加作用は野生型と同等であるが[1)]，低用量メタンフェタミン反復投与では逆耐性現象が形成されなかった[30)]。NET-KOマウスではコカイン投与による移所運動量増加作用は野生型に比べて増加していたが，反復投与による逆耐性は形成されなかった[36)]。これらの結果からは5-HTまたはノルエピネフリン（NE）神経伝達過剰状態では逆耐性の形成は抑制される可能性が示唆された。

従来の薬理学的研究ではD1拮抗薬により逆耐性現象が抑制される結果が報告され，逆耐性の形成にはD1受容体活性化が必須であるとされてきたが，拮抗薬の受容体特異性の問題があった。D1-KOマウスで検討された結果，コカイン，メタンフェタミンによる急性運動刺激作用は減弱していたが逆耐性現象は形成された。また，コカインの報酬効果は保たれていた[9)]。この結果からは，D1受容体の活性化は逆耐性，報酬効果形成に必須ではないかあるいはD1-KOマウスでは何らかの代償機構が働いている可能性が推察された[20)]。D1受容体familyに属するD5受容体のKOマウスの中枢刺激薬に対する検討はなされていない。D2-KOマウスではモルヒネの報酬効果は減弱しており[7)]，依存形成にはD2受容体活性化が重要であるかと思われたが，コカインの自己投与行動は保たれ，依存が形成された[3)]。D2受容体familyであるD3，D4受容体のKOマウ

スではコカインの運動刺激効果は増強しており[16)37)]，これらの受容体活性化は運動刺激に対し抑制的に働くことが示唆された。D3-KOマウスではメタンフェタミンの報酬効果は増強しており[37)]，D3受容体活性化は依存形成に対しても抑制的に働く可能性があるが，D2，D3，D4-KOマウスでの逆耐性現象については報告がない。DA受容体欠損マウスでは一つのサブタイプが欠損してもfamilyに属する他のサブタイプが代償する可能性もあり，今後，複数のサブタイプを欠損したダブル・トリプルKOマウスでの検討も必要と考えられる。

4．統合失調症の病態指標としてのプレパルスインヒビション（PPI）

突然の強力な聴覚，視覚または触覚刺激に出会うとヒトを含めさまざまな動物は，顔面や全身の筋肉のすばやく短い痙攣様の反応を示す。我々は，この生理学的現象を驚愕反応と呼び，外部からの侵害的な刺激に対する防衛的機能の一つであると考えている[5)]。驚愕反応は，条件付け，感作，馴化，薬剤投与などにより増減する特徴を有するが，なかでもPPIにおける驚愕反応減弱現象は，統合失調症で障害されていることから注目を集めている[2)]。PPIとは，驚愕刺激を与える直前（一般的には30～500 ms前）に，それ自体では驚愕反応を引き起こさない程度の弱い刺激（プレパルス）をあらかじめ負荷することで驚愕反応の強度が低下する現象である。他の精神生理学的パラダイムと比べ，PPIの利点は実験動物においても同様のパラダイムを問題なく適応できる点にある。

我々は，DAが過剰であるDAT-KOマウス，5-HTが過剰なSERT-KOマウス，DAと5-HT双方が過剰なDAT/SERTダブルKOマウスにおいてPPIを検討した。DAT-KOマウスでは野生型に比べてPPIが減弱していた。DAT-KOマウスでみられるPPIの減弱は4週齢から9週齢までで顕著に認められた。一方，SERT-KOマウスとDAT/SERTダブルKOマウスではPPIが正常だったので，DAT-KOによるPPIの障害はSERT-KOが加わると回復することがわかった。DAT-KOマウスにD2受容体拮抗薬を投与するとPPIの障害が回復することから[14)]，DAT-KOマウスにおけるPPIの障害はDA*ex*の増加によるDA神経伝達のtonicな変化が原因であり，アンフェタミン等の間接的DA作動薬投与によるPPI障害[15)]と同様の機序が働いていると推定した。これに対して，SERT-KOマウスではPPIの障害を認めなかった。SERT-KOマウスでも，DAT-KOマウスと同様に，線条体における5-HT*ex*は野生型マウスの約10倍に達する[30)]。マウスにおいて，5-HT放出薬であるMDMA（3，4-メチレンジオキシメタンフェタミン）等の投与はPPIを障害すると報告されており[4)]，5-HT神経伝達過剰がPPIを引き起こす可能性がある。しかし，選択的セロトニン再取り込み阻害薬であるフルオキセチンではPPIの障害を認めなかった[8)]。これらの報告と我々の結果から，マウスにおいて5-HT*ex*の過剰のみではPPIの障害を認めない，あるいは，生来的な5-HT過剰による5-HT受容体の変化を含む5-HT神経伝達の適応的変化によりPPIが正常化した可能性が示唆された。MDMA等のPPI障害効果は，5-HT*ex*過剰効果だけによるものではなく，DA系神経伝達変化等の相互作用が絡んでいる可能性も考えなければならないだろう。次に，DAT/SERTダブルKOマウスであるが，野生型マウスと比較して有意なPPI障害を認めなかった。DAT/SERTダブルKOマウスのDA*ex*，5-HT*ex*はいずれも野生型マウスの約10倍である[30)]。上述した，DA*ex*の増加によるDA神経伝達の過剰によりPPIの障害が起こるという仮説が正しいならば，この状態に，5-HT*ex*上昇が加わることによって，PPIの変化が引き起こされたと推察される。DA神経伝達過剰かつ5-HT神経伝達過剰の状態にあるマウスのPPIには，感覚運動情報制御におけるDA系と5-HT系の神経伝達の変化と相互作用が関与している可能性が予想された[10)]。

5．おわりに

精神疾患の「作業仮説」を検証する上で，ノッ

クアウトマウスを含む遺伝子改変動物は有用なモデル動物であると考えられる。精神疾患は，単一の遺伝子の異常によるものではなく，複数の遺伝子が脆弱性を形成し，遺伝要因と環境要因が複雑に関与して発症すると考えられている。当教室では，複数の遺伝子が関与していると考えられる精神疾患の病態の解明に，進展の著しいヒトゲノム計画などから得られる情報を大いに活用し，ヒトとモデル動物から得られる知見を相互にフィードバックさせて取り組んで行きたい。なお，本稿では紹介できなかったオピオイド神経伝達に関する研究等は当教室のホームページ：http：//www.psychobio.med.tohoku.ac.jp をご参照いただきたい。

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Target dependency of brain mechanism involved in dispositional inference: a PET study

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The cognitive mechanism for inference of personal dispositions, such as personality traits and abilities, is postulated to be dependent on the amount of episodic memory concerning target persons. To examine whether there is such target dependency in the brain mechanism during dispositional inference, we measured brain activity of normal volunteers while they were performing seven dispositional inference tasks, each for a target person in different categories, using positron emission tomography (PET). Effect of the target-person category on activation was significant in the posterodorsal, polar, and ventral subdivisions of medial prefrontal cortex, right orbitoinsular junction, left temporal pole and superior temporal sulcus, cerebellum, and thalamus, suggesting the existence of target dependency in activation during dispositional inference. The amount of episodic memory concerning a target person measured using the self-evaluative questionnaire was positively correlated with the activation in the polar subdivision of the medial prefrontal cortex, and negatively with that in a region in the left superior temporal sulcus. Together with the available knowledge on the functional roles of these regions and the proposed cognitive model in social psychology, our results suggest that these two regions play roles supplementary to each other in dispositional inference; a region in the superior temporal sulcus is involved in the processing of relevant episodic exemplar and the polar subdivision of the medial prefrontal cortex in the processing of summarized value information about the target person.
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Introduction

In interpersonal relationships, it is often wise to choose one's behavior depending on the person who confronts one, because the reaction to the behavior varies depending on personal dispositions, such as personality traits and abilities, and the current mental state, such as intention and desire, of the person. Therefore, the correct inference of the personal dispositions and the current mental state provide one an advantage in interpersonal relationships. The necessity of such a social inference is so ubiquitous in our daily life, and its ability is essential for one's social survival. The cognitive mechanism of inference of the other individual's mental state is conceptualized as "Theory of Mind" (Leslie, 1987; Premack and Woodruff, 1978), and its brain mechanism has been studied in many functional imaging studies (Brunet et al., 2000; Castelli et al., 2000; Fletcher et al., 1995; Gallagher et al., 2000; Goel et al., 1995; Vogeley et al., 2001). The cognitive mechanism of dispositional inference has also been paid considerable attention in social psychology; however, only a few functional imaging studies have dealt with its brain mechanism indirectly (Craik et al., 1999; Zysset et al., 2002, 2003).

The cognitive mechanism of dispositional inference, particularly the role of episodic memory, has been a matter of debate among social psychologists for several decades. Some argued that dispositional inference is made by retrieving memories of a target person's past behavior relevant to disposition (behavioral exemplar) (Kahneman and Miller, 1986; Rywick and Schaye, 1974; Smith and Zarate, 1992). Others argued that knowledge of personal disposition is abstracted from multiple experiences with disposition-relevant behaviors of the target person and represented in the summary form (summary knowledge) (Buss and Craik, 1983; Hampson, 1982). Recent researches have suggested that both sources of memory (behavioral exemplar and summary knowledge) are used for dispositional inference, and the extent to which each source is used depends on several factors, including the amount of experienced disposition-relevant behavior (Klein et al., 1992). Other researchers have suggested that emotion also influences dispositional inference. It has been shown that the judgment of disposition is affected by emotion or mood at the time when a relevant behavior is encoded (Fielder et al., 1991; Forgas and Bower, 1987) and when a dispositional inference is made based on the memorized behavior (Forgas, 1992). Needless to say, the amount of available episodic memory and the emotional state vary among different people. If the amount of available episodic memory and the emotional state thus affect the mental operation of dispositional inference, it is reasonable to consider

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that the brain mechanism participating in dispositional inference depends on the target person. This possible target dependency has to be taken into account when functional imaging study on the dispositional inference is intended.

In this study, using a functional imaging technique, we attempted to reveal the brain mechanism of dispositional inference, focusing our attention to its target dependency. Nine normal subjects performed seven dispositional inference tasks, each toward a different target person, and two control tasks. The lineup of the target-person categories was so selected such that the amount of available episodic memory and the emotional state concerning the target person would largely vary. Their brain activity during each task was measured using $H_2^{15}O$-PET. We first identified brain areas significantly activated during the dispositional inference tasks, and examined whether activation in each area significantly varies across the target-person categories. Second, we attempted to specify the factors that explain the observed difference in the activation pattern among the target-person categories. Although previous studies in social psychology have suggested the amount of available episodic memory and the emotional state concerning the target person as major factors that affect cognitive operation of dispositional inference, such studies have not provided any practical way to measure these factors in naturalistic people. Episodic memory and emotion are closely related to each other in real interpersonal relationships, and it may be problematic to measure them as independent factors. Therefore, we constructed a self-evaluative questionnaire composed of many items each measuring a specific aspect of personal relationships, particularly concerning the amount of available episodic memory and the emotional state concerning a target person. Each subject completed this questionnaire for each target person, and a principal component analysis (PCA) was applied to the data to extract a small number of independent factors. The measures for these factors (principal component scores) were used in multiple regression analysis of the positron emission tomography (PET) data to detect a brain region whose activation is explained by each factor. Interpretation of the extracted factors and the result of multiple regression analysis of the PET data will be discussed in comparison with the proposed cognitive mechanism of dispositional inference in the previous studies in social psychology.

Methods

Subjects

Nine right-handed normal Japanese male volunteers (ages 18–21 years) participated in this study. All were undergraduate students of Tohoku University, Sendai. None had a history of neurological or psychiatric disease. Handedness was assessed using the Edinburgh Inventory (Oldfield, 1971). Written informed consent was obtained from each subject according to the Declaration of Helsinki and the guidelines approved by the Ethical Committee of Tohoku University.

Tasks and stimuli

Each subject performed nine tasks. Seven of the tasks were dispositional inference tasks. Before each dispositional inference task, a target person, about whom a dispositional inference would be required, was assigned. In each trial of the dispositional inference task, a Japanese word or phrase of personal disposition, such as "honest", "tall", or "runs fast", with the color of the characters in red, yellow, or blue, was presented for 1 s at the center of the visual field, followed by a 2-s presentation of a fixation cross. Each subject was required to determine whether each presented word or phrase was an appropriate description of the target person. "Appropriate", "Not appropriate", and "Cannot say either" were the three possible responses, and each subject responded by pressing one of the three buttons on a small box held in his right hand. A different target person was assigned in each dispositional inference task; each of the seven target persons was in each of the following seven target-person categories: a character in a comic book that each subject read 30 min before the PET experiment (Comic), a favorite famous person (Famous), a current friend (NewF), an old friend (OldF), a sibling (Sibling), the subject's father (Father), and the subject himself (Self). When more than one person were available as target persons in a category, that is, either in the Famous, NewF, OldF, or Sibling category, the subject was required to specify one in his mind before the task started. The remaining two tasks were the control tasks. One was a color judgment task (Color), in which the stimulus presentation was the same as in the dispositional inference tasks, but the subject was required to discriminate the color of characters in each presented word or phrase; this task was a control for the low-level visual input and motor output of the dispositional inference tasks. Another was a rest task (Rest), in which the subject was required to focus his eyes on the fixation cross presented at the center of the visual field and to try to avoid any thinking; this task was a baseline task. The order of the nine tasks was counterbalanced among the nine subjects.

In each dispositional inference task and the Color task, 40 stimuli were presented during a 120-s task period. From a pool of more than 500 words or phrases of personal disposition, 320 stimuli were selected eliminating those with difficult meanings or those that implied a disposition of people in a specific target-person category, based on the results of a preliminary study using 20 normal subjects other than those who participated in the present PET study. These 320 stimuli were divided into eight sets (40 stimuli in each set), controlling the mean numbers of characters among the eight sets and avoiding clustering of words/phrases with similar meanings or emotional valences. Each stimulus set was used once in each of the eight tasks for each subject. The combinations of the stimulus set and the target-person category were counterbalanced among the nine subjects.

After all the tasks were completed, the subject was required to perform all the dispositional inference tasks again outside the PET scanner. In this second execution of the dispositional inference tasks, each subject was encouraged to make as good inference as possible without any time constraints. The response in the second execution outside the PET scanner was regarded as "correct" and used as a reference to determine the correct response in the first execution inside the PET scanner.

Self-evaluation of memory and emotion concerning the target person

Each subject self-evaluated the amount of memory and/or the emotional state concerning all the target persons except for the Self. Each subject performed it immediately after each dispositional inference task inside the PET scanner while waiting for the decay of radioactivity. The items were visually presented and each subject responded using buttons for the tasks. The questionnaire, composed of 23 items (Table 1), was constructed by the

Table 1
Items of the self-evaluative questionnaire

No.	Items	PCA loadings	
		First PC	Second PC
1	I have a loving memory of this person.	0.234	0.251*
2	I have a joyful memory of this person.	0.250	0.222
3	I have an exasperating memory of this person.	−0.010	0.359*
4	I have a fearful memory of this person.	−0.034	0.337*
5	I have a sad memory of this person.	0.040	0.279*
6	I have a memory of this person.	0.199	0.290*
7	I feel love when I think of this person.	0.226	0.139
8	I feel joy when I think of this person.	0.269*	−0.054
9	I feel anger when I think of this person.	−0.231	0.238
10	I feel fear when I think of this person.	−0.204	0.201
11	I feel sad when I think of this person.	−0.203	0.233
12	I feel love when I am with this person.	0.257*	0.096
13	I feel joy when I am with this person.	0.278*	−0.046
14	I feel anger when I am with this person.	−0.224	0.210
15	I feel fear when I am with this person.	−0.161	0.233
16	I feel sad when I am with this person.	−0.237	0.133
17	I like this person.	0.274*	−0.102
18	I hate this person.	−0.238	0.129
19	I have knowledge of this person.	0.177	0.191
20	I can visually imagine this person.	0.151	0.188
21	I feel intimate with this person.	0.255*	−0.018
22	I have influenced this person.	0.158	0.250
23	This person has influenced me.	0.170	0.143

The items were originally in Japanese. The loadings for the first and second principal components (PCs) are shown for each item.
*For the five loadings with the largest absolute values for each PC.

authors for the purpose of this study, attempting to include as many factors as possible concerning memory and emotion that have been assumed to affect cognitive operation of dispositional inference. Six items measured the amount of episodic memory (I have a... memory of this person), five of which were about emotion-laden episodes and one was about episodes without emotion. Five items measured the extent of the emotional experience during recollection of the episodes (I feel... when I think of this person). Five items measured the extent of the emotional impression toward the target person that was not related to past episodes (I feel... when I am with this person). For each category of those emotion-related items, the five basic emotions, namely, love, joy, anger, fear, and sadness (Shaver et al., 1987), were adopted. Two items measured the extent of a more general emotional impression toward the target person (like and hate). There were also items that measured the amount of knowledge and visual image, and the extent of intimacy, and items that evaluate uncategorized personal relationships. Each item was scored using a five-grade scale (1: none at all–5: very much).

PET measurements

PET measurements were performed using a SET-2400W PET scanner (Shimadzu, Kyoto, Japan) (Fujiwara et al., 1997) following a bolus injection of $H_2^{15}O$ (200 MBq). Each subject was positioned comfortably on the bed of the PET scanner, wearing a face-mounted display (Eye-treck FMD011F, Olympus, Tokyo). Emission data collection (3D mode) was started immediately after cortical radioactivity was observed, and it lasted 60 s. The beginning of the task was adjusted such that the emission data collection started approximately 20 s after the task began.

Image preprocessing

All the image processing procedures, except for those that were specified, were performed using statistical parametric mapping (SPM) 99 software (Wellcome Department of Cognitive Neurology, London, UK) implemented on MATLAB (Mathworks, Inc., Natick, MA). Whole-brain T1-weighted MRI was acquired for each subject on a separate occasion for the purpose of spatial normalization of the PET images. The MRI of each subject was anatomically normalized to the standard brain of the Human Brain Atlas (Roland et al., 1994) for each subject using the Automated Image Registration (Woods et al., 1998) and Elastic Transformation (Schormann et al., 1996, 1999). The calculated transformation parameter was then applied to the PET images following the adjustment for head movements and coregistration to the MRI, in each subject. All the normalized PET images were smoothed with a Gaussian kernel of 16 mm full-width at half maximum (FWHM). Proportional scaling of the voxel value into the global mean cerebral blood flow (CBF) of 50 ml/dl/min was performed before each statistical analysis.

Activation during the dispositional inference task in each target-person category

We performed conventional subtraction analysis to determine brain regions with significant activation during dispositional inference task in each target-person category. A voxel-by-voxel two-way ANOVA was performed implementing the task effect (nine tasks) as a condition of interest and the subject effect as a condition of no interest. Subsequently, using a t test, the estimated effect of dispositional inference task in each target-person category was compared with that of the Color task ($P < 0.001$, uncorrected) masked by the comparison with that of the Rest task ($P < 0.05$, uncorrected) to avoid false activation due to deactivation in the Color task.

To examine whether each activated area exhibits target-person dependency of activation, a significance of the effect of the target-person category was tested. This was achieved

Table 2
Performance data

Task	Color	Comic	Famous	NewF	OldF	Sibling	Father	Self
Correct responses (%)	98.6 ± 1.8	66.9 ± 10.2	76.1 ± 14.4	70.0 ± 12.3	74.4 ± 13.6	74.2 ± 10.8	72.5 ± 8.8	75.0 ± 14.0
Reaction time (ms)	1061 ± 182	1602 ± 172	1466 ± 162	1526 ± 173	1426 ± 174	1494 ± 179	1514 ± 147	1435 ± 166

The mean percentages of the correct responses and the mean response times in the Color task and the dispositional inference tasks for the seven target-person categories are shown. Values are means ± standard deviations.

Table 3
Activated areas in the dispositional inference task for each target-person category

Structure	Comic	Famous	New	Old	Sibling	Father	Self
Medial prefrontal cortex							
Anterodorsal	6,48,36 (4.51)	6,51,40 (4.67)	15,58,38 (3.29)	3,49,38 (5.10)*	3,49,38 (5.49)*	2,46,41 (4.65)	
	−3,43,49 (4.58)		−2,38,55 (3.85)		−2,32,56 (5.39)	−2,38,56 (4.96)	−1,38,53 (4.89)*
Posterodorsal		8,20,62 (4.31)		3,12,61 (3.79)	2,12,59 (4.04)		2,16,62 (3.46)
Polar			−4,59,16 (4.23)	−3,56,19 (5.50)*	−1,55,28 (5.54)*	−2,−56,21 (4.86)	−1,58,25 (4.99)*
Ventral	4,58,5 (3.55)			0,56,6 (6.10)*	−1,55,4 (4.26)		
Anterior cingulate	8,32,40 (3.73)	3,30,39 (3.67)		12,20,46 (4.86)			
L. ventrolateral prefrontal cortex	44,32,4 (4.71)	49,29,11 (3.33)	45,33,6 (3.62)	41,30,2 (4.09)	43,30,6 (4.50)	45,32,8 (3.80)	
					44,27,23 (4.45)		
L. orbitoinsular junction		34,23,−8 (4.38)		32,22,−8 (4.62)	32,29,−6 (4.18)		
R. orbitoinsular junction		−31,23,−6 (3.61)		−35,23,−7 (3.48)			
L. temporal pole	48,12,−22 (4.31)	50,16,−18 (3.47)		48,13,−15 (3.42)			
L. superior temporal sulcus	48,−20,−4 (3.80)						
Cerebellum		11,−43,−27 (3.53)	−1,−49,−11 (3.85)		0,−46,−11 (4.39)		1,−51,−9 (3.74)
Thalamus		2,−16,0 (4.23)		0,−4,1 (5.40)*	−1,−13,1 (5.04)*	0,−16,1 (4.33)	
Midbrain							0,−17,−6 (3.60)

Talairach coordinates and the T score (in parentheses) of the peak activation are shown for each significantly ($P < 0.001$, uncorrected) activated area during the dispositional inference task compared with the Color task for each target-person category. Each activation was masked with the comparison with the Rest task to avoid the false activation caused by deactivation during the Color task.
* Survives a correction for multiple comparisons ($P < 0.05$). Activated areas in the medial prefrontal cortices are separated into the following four arbitrary subdivisions according to the Talairach coordinates: anterodorsal ($y \geq 30$, $z \geq 30$), posterodorsal ($y < 30$), polar ($10 \leq z < 30$), and ventral ($z < 10$). R: Right, L: Left.

by testing whether omission of all the regressers for the target-person categories from the model used in the two-way ANOVA would significantly increase residual variance or not, using an F test (Friston et al., 1995). An F score image was made masked by the results of the mean of all the dispositional inference tasks versus the Color task, and that versus the Rest task ($P < 0.05$, uncorrected). Having varied locations of the activation peaks in each activated area across the

Table 4
Areas showing significant effect of the target-person category

	Talairach coordinate (F score)
Medial prefrontal cortex	
Posterodorsal	−6,26,60 (2.98)
Polar	−6,55,22 (3.89)
Ventral	−2,59,4 (2.55)
R. orbitoinsular junction	−33,22,−15 (3.18)
L. temporal pole	48,9,−21 (2.82)
L. superior temporal sulcus	50,−22,−5 (3.43)
Cerebellum	11,−43,−25 (3.06)
Thalamus	6,−20,4 (4.34)

Talairach coordinates and the F score (in parentheses) of the peak voxel are shown for each of the significantly activated areas in the dispositional inference task for any of the target-person categories, in which effect of the target-person category was significant ($P < 0.05$, uncorrected) in F test. Other details are the same as in Table 3.

Table 5
Results of regression analysis with principal component scores

	First PC	Second PC	
	Positive	Positive	Negative
Medial prefrontal (*polar*)		−3,55,23 (7.08)	
L. superior temporal sulcus			62,−7,2 (3.84)
Thalamus	−10,−22,0 (5.24)	−14,−20,11 (5.87)	

Talairach coordinates and the T score (in parentheses) of the peak voxel are shown for each area in which positive or negative correlation between the brain activity and the principal component score was significant ($P < 0.005$, uncorrected) across all the subjects. The search area was confined to the significantly ($P < 0.05$, uncorrected) activated areas in the dispositional inference task on average compared with the Color and Rest tasks. Other details are the same as in Table 3.

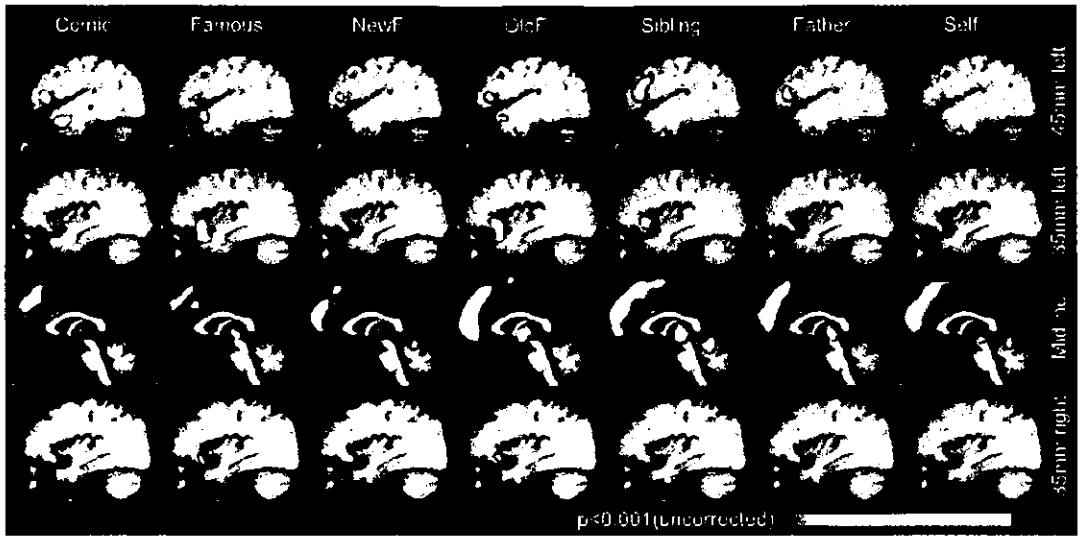

Fig. 1. Areas showing significant activation in the dispositional inference task for each target-person category compared with the Color task ($P < 0.001$, uncorrected) are overlaid on the mean normalized anatomical T1-weighted MRIs of all the subjects. Four sagittal slices: 45 and 35 mm left from the midline, on the midline, and 35 mm right from the midline are shown for each target-person category from top to bottom. Each activation is masked with the comparison with the Rest task ($P < 0.05$, uncorrected).

target-person categories, significance ($P < 0.05$, uncorrected) in the F test was determined based on the visual inspection of each area.

Exploration of factors that explain the target dependency of activation

The scores for each item of the self-evaluative questionnaire were normalized to mean = 0 and variance = 1 across the six target persons within each subject. A correlation matrix for the 23 items (23 × 23 matrix) was then constructed using the normalized scores for all the pooled target persons across all the subjects (9 subjects × 6 target persons = total 54 target persons). A PCA was applied to the correlation matrix using MATLAB. A few principal components with large proportions were regarded as meaningful factors; the number of the meaningful factors was determined according to the proportion. The meaning of each factor was interpreted according to the loadings of the 23 items. A principal component score for each target person was calculated for each factor as a linear conjunction of the normalized scores weighted with the loading of each item; the score was regarded as a summary measure of each factor in each target person.

To explore the brain regions whose activation during the dispositional inference tasks was correlated with the principal component scores for each factor, voxel-by-voxel multiple regression analysis was performed in each subject, implementing the principal component scores for all the factors. Because both the principal component scores and brain activity were normalized within each subject, the analysis can be regarded as a correlation analysis between the scores and brain activation against any baseline. Statistical inference was made for each factor according to a random effects model, using voxel-by-voxel one-sample t test of the parameter estimates from all the subjects. Because the search area was confined to the activated areas in the subtraction analysis, by masking with the results of the mean of all the dispositional inference tasks versus the Color task, and that versus the Rest task ($P < 0.05$, uncorrected), $P < 0.005$ (uncorrected) was adopted as a threshold.

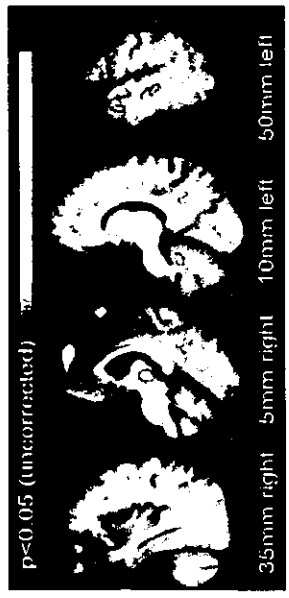

Fig. 2. Areas showing significant effect of the target-person category (F test: $P < 0.05$, uncorrected). Activation was masked by the results of the mean of all the dispositional inference tasks versus the Color task, and that versus the Rest task ($P < 0.05$, uncorrected). Four sagittal slices: 50 and 10 mm left, and 5 and 35 mm right from the midline are shown from top to bottom. Other details are the same as in Fig. 1.

Results

Performance data

The mean percentages of the correct responses and the mean response times in the Color task and dispositional inference tasks in the seven target-person categories are given in Table 2. The effect of the tasks was significant in both the performance parameters ($P < 0.05$, F test in two-way ANOVA). The mean percentage of correct responses was significantly lower and the mean response time was significantly longer in the dispositional inference task in any target-person category than in the Color task ($P < 0.05$, corrected for multiple comparisons), but no significant difference was found in either parameter among the seven target-person categories.

Activation during the dispositional inference task in each target-person category

Significant activation during the dispositional inference task compared with the Color task for each of the seven target-person categories is shown in Table 3 and Fig. 1. Marked activation was observed in the medial prefrontal cortex for all the target-person categories, but its spatial extent varied considerably among the target-person categories. Having no established anatomical landmarks that subdivide these areas, we adopted arbitrary subdivisions according to the Talairach coordinate (see legend in Table 3). Activation was observed in the anterodorsal subdivision for all the target-person categories, but it was observed in the posterodorsal subdivision only for the Famous, OldF, Sibling, and Self; in the polar subdivision for the NewF, OldF, Sibling, Father, and Self; and in the ventral subdivision for the Comic, OldF, and Sibling. Activation was also observed in the adjacent anterior cingulate cortex for the Comic, Famous, and NewF. The left ventrolateral prefrontal cortex was activated for all the target-person categories except for the Self. Activation in the orbitoinsular junction was observed bilaterally for the Famous and OldF, and only in the left hemisphere for the Sibling. Activation in the left temporal pole was observed for the Comic, Famous, and Old, and in the left superior temporal sulcus for the Comic. Activation in the cerebellum was observed for the Famous, New, Sibling, and Self; in the thalamus for the Famous, Old, Sibling, and Father; and in the midbrain for the Self.

The results of the F test for the effect of the seven target-person categories are shown in Table 4 and Fig 2. The effect of the target-person categories was significant in all the subdivisions of the medial prefrontal cortices except for the anterodorsal subdivision. It was also significant in the anterior cingulate, the right orbitoinsular junction, the left temporal pole, the left superior temporal sulcus, the cerebellum, and the thalamus.

Factors that explain the target dependency of activation

The PCA for the items of the self-evaluative questionnaire gave two principal components (PCs) with markedly large proportions (37.9% and 23.0% for the first and second PCs, respectively) compared with those of the rest of the principal components (e.g., 6.2%, 5.1%, and 4.0% for the 3rd, 4th, and 5th PCs, respectively). Therefore, the first and second PCs were regarded as meaningful factors. The loadings of each item on the two PCs are shown in Table 1. The relationship between each item and the two PCs are illustrated by plotting the loading for the second PC against that for the first PC in Fig. 3a. For the first PC, the five items with the largest absolute values of the loadings were "I feel joy when I am with this person" (item 13), "I like this person" (item 17), "I feel joy when I think of this person" (item 8), "I feel love when I am with this person" (item 12), and "I feel intimate with this person" (item 21), all with positive loadings. Most of the items with positive loadings for the first PC were those evaluating the aspects accompanying positive emotions, and all with negative loadings were those evaluating the extent of negative emotions during recollection of the episodes (I feel... when I think of this person), and the emotional impression toward the target person that was not related to past episodes (I feel ... when I am with this person). For the second PC, the five items with the largest absolute values of the loadings were "I have an exasperating memory of this person" (item 3), "I have a fearful memory of this person" (item 4), "I have a memory of this person" (item 6), "I have a sad memory of this person" (item 5), and "I have a loving memory of this person" (item 1), all with positive loadings. On the whole, the second PC appeared to be characterized by the items evaluating the amount of episodic memory, either with or without emotion, ranking high in the list of items with the larger positive loadings for the second PC, particularly those bearing negative emotions (items 3, 4, and 5), which showed little loadings for the first PC. In terms of possible correlation or interaction between the amount of episodic memory and the emotional state, it appears noteworthy that the items evaluating the amount of episodic memory with positive emotion or without emotion (items 1, 2, and 6) also had considerable loadings for the first PC.

The principal component score calculated from the loadings and the normalized scores for all the items for each target person for each subject for each PC are shown in Fig. 3b. Some trend among the target-person categories and its considerable intersubject variability were both observed. The results of the intersubject analyses of the regression analyses are given in Table 5 and Fig. 4. A positive regression coefficient between brain activity and the principal component score for the first PC was significant in the thalamus (Fig. 4a). No area showed a significant negative regression coefficient for the first PC. A positive regression coefficient between brain activity and the principal component score for the

Fig. 3. (a) Two-dimensional illustration of the relationships between each item and the two PCs are shown. For each item, the loading for the second PC (vertical axis) is plotted against that for the first PC (horizontal axis). See Table 1 to refer the item number (in each circle) to the item sentence. (b) The principal component scores for the first PC (left panel) and second PC (right panel). The scores for the six target persons are shown for each subject (a specific symbol connected with a specific line), for each PCs. Note that the overall mean of the scores for each PC equals zero because they were generated from the normalized self-evaluated scores.

Fig. 4. (a) An area showing significant positive regression between activation and the principal component score for the first PC. Areas showing significant positive (b) and negative (c) regressions between activation and the principal component score for the second PC. Coronal and sagittal slices through activated area(s) are shown for each analysis. The positive and negative regressions ($P < 0.005$, uncorrected) are shown in red-yellow and blue-cyan color scales, respectively. Other details are the same as in Fig. 1.

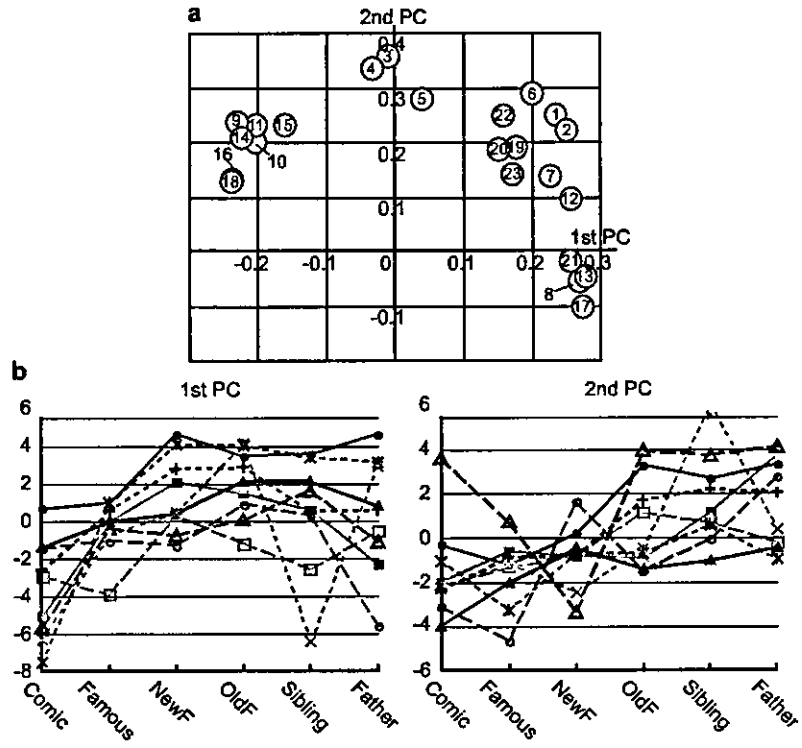

Fig. 3.

second PC was significant in the polar subdivision of the medial prefrontal cortex and the thalamus (Fig. 4b). Negative regression between brain activity and the principal component score for the second PC was significant in the left superior temporal sulcus (Fig. 4c).

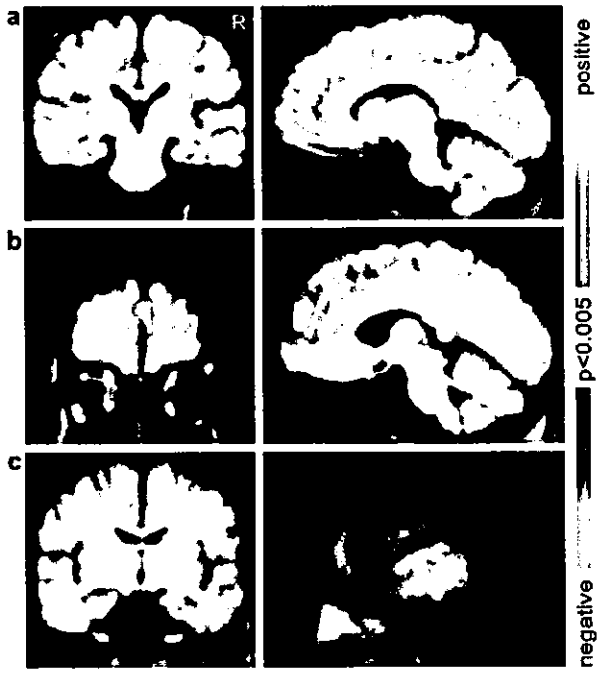

Fig. 4.

Discussion

During the dispositional inference tasks, significant activation was observed in several brain areas, including the medial and left ventrolateral prefrontal cortices, the bilateral orbitoinsular junctions, the left temporal pole, the left superior temporal sulcus, and the thalamus, with considerable variability among the target-person categories. On the whole, the lineup of the activated areas were similar to those observed in previous functional imaging studies that adopted similar tasks (Craik et al., 1999; Zysset et al., 2002, 2003), as well as those observed in studies on the Theory of Mind (Brunet et al., 2000; Castelli et al., 2000; Fletcher et al., 1995; Gallagher et al., 2000; Goel et al., 1995; Vogeley et al., 2001) and other social judgments (Farrow et al., 2001; Moll et al., 2001, 2002), suggesting that these social judgments share largely the same brain mechanisms. The striking finding was, however, the variability of the observed activation patterns across the target-person categories. The effect of the target-person category was significant in the *F* test on the posterodorsal, polar, and ventral subdivisions of the medial prefrontal cortex, the right orbitoinsular junction, the left temporal pole, the left superior temporal sulcus, the cerebellum, and the thalamus. Besides the result of the *F* test, the difference in the activation pattern during the dispositional inference task between the Comic and Self (Fig. 1) is sufficiently convincing that studies based on the models ignoring the effect of a target dependency would produce highly inconsistent results. The observed activation patterns in the Famous and Self are

similar to those during the tasks similar to our dispositional inference task for a prime minister and for the subject oneself, respectively, in the study by Craik et al. (1999), although they have not shown statistically significant difference. The results clearly supported the assumption that there is target dependency in the brain activation pattern during the dispositional inference tasks, although it does not necessarily mean that the critical mechanism for the task execution is target-dependent.

The PCA extracted two independent factors in the interpersonal relationship with the target persons from the data of the self-evaluative questionnaire. The first PC appears to measure emotional valence (positive–negative), and the second PC the amount of episodic memory. The items evaluating the amount of episodic memory with positive emotion or without emotion (items 1, 2, and 6) showed positive large loadings not only for the second PC but also for the first PC. This suggests that there is interaction between the self-evaluation of the amount of episodic memory and that of the emotional state; therefore, the second PC should be regarded as an orthogonalized measure of the amount of episodic memory against the first PC. The results of regression analyses between the PET data and the principal component scores showed that in three brain regions, the observed target dependency of brain activity is explained by these two factors. Activation in the thalamus was positively correlated with the principal component scores of both the PCs. Activation in the polar subdivision of the medial prefrontal cortex was positively correlated with the principal component score of the second PC, and that in the left superior temporal sulcus correlated negatively. Considering the cognitive model of dispositional inference proposed by Klein et al. (1992), the observations concerning the second PC would be particularly interesting. It was argued that "At low levels (little amount) of relevant experience, trait knowledge is represented only at the level of behavioral exemplar, but with sufficient experience, trait knowledge will be abstracted from exemplars and represented in summary form (summary knowledge)" (Klein et al., 1992). It is reasonable to assume that the amount of episodic memory positively correlates with the amount of the opportunities of abstracting personal dispositions into a summary form. Then, the results can be interpreted as that the region in the left superior temporal sulcus is more involved when one has less experience of episodes, thus judgment has to be made according to the behavioral exemplar. On the contrary, the polar subdivision of the medial prefrontal cortex is more involved when the disposition of the target person is sufficiently abstracted in a summary form through enough experience of the episodes associated with the target person. The results of previous functional imaging studies have frequently suggested the role of the region in the superior temporal sulcus or its proximity in the perception of biological motion, including body (Bonda et al., 1996; Grossman et al., 2000; Howard et al., 1996), hand (Bonda et al., 1996; Grafton et al., 1996; Grezes et al., 1999; Rizzolatti et al., 1996), eye (Puce et al., 1998; Wicker et al., 1998), and mouth movements (Puce et al., 1998). Reports of activation in this region by static views of body parts (Haxby et al., 1999; Hoffman and Haxby, 2000; Kanwisher et al., 1997; Kourtzi and Kanwisher, 2000), and by several social judgment tasks (Brunet et al., 2000; Castelli et al., 2000; Moll et al., 2001, 2002; Winston et al., 2002; Zysset et al., 2003) has, however, shifted the notion of the role of this region to social perception (see Allison et al., 2000, for review). Activation in the polar subdivision of the medial prefrontal cortex has been reported in a wide variety of tasks, such as emotional experience (George et al., 1995; Lane et al., 1997b; Pardo et al., 1993; Teasdale et al., 1999), experience of sensation (Blakemore et al., 1998), recognition of famous, or personally familiar faces (Gorno-Tempini et al., 1998; Leveroni et al., 2000; Sugiura et al., 2001), challenging the conceptualization of the role of this region. Recent researchers appear to prefer the concept of "self-referential or introspectively oriented mental activity" as a comprehensive explanation of the role of this region (Gusnard et al., 2001), supported by the results of functional imaging studies that activity of this region is higher during explicit attention to one's own emotional state than during an implicit task (Gusnard et al., 2001; Lane et al., 1997a), and during evaluative judgment concerning past episodes than during a simple episodic retrieval task (Zysset et al., 2002). A previous PET study showed that the medial prefrontal cortex corresponding to our polar subdivision exhibited activity during judgment tasks higher for autobiographical episodes than for other types of memory, but the area close to the left superior temporal sulcus was equally involved in the judgment tasks irrespective of the type of memory (Maguire and Mummery, 1999). Together with these previous findings, the results suggest that the two regions play supplementary roles each other in the dispositional inference. The region in the superior temporal sulcus is involved in the extraction of information relevant to the disposition from the retrieved specific episode (episodic exemplar), and the polar subdivision of the medial prefrontal cortex directly processes value information of the target person (summary knowledge) independent of any specific episodes, possibly based on a process involving introspection. This interpretation is congruent with highly significant activation in the polar subdivision of the medial prefrontal cortex and the absence of significant activation in the superior temporal sulcus in the Self task, data of which were not included in the regression analyses using the principal component scores. The results of the PCA on the self-evaluative questionnaire and the regression analysis thus suggest that the observed target dependency of the activation pattern reflects the target dependency of the cognitive mechanism of the dispositional inference. On the other hand, activation in the thalamus positively correlates with the principle component scores for both the PCs, which makes it difficult to address meaningful discussion on the role of the thalamus in dispositional inference.

The results are also interesting as regards the functional organization of the medial prefrontal cortex. The anterodorsal subdivision was activated in all the target-person categories with no target dependency, and the polar subdivision demonstrated marked target dependency. This suggests that there are at least two different functional modules concerning the dispositional inference in the medial prefrontal cortex. In previous functional imaging studies of the Theory of Mind and other social inference tasks, the locations of the activation peaks in the medial prefrontal cortex were scattered over the two subdivisions (Brunet et al., 2000; Castelli et al., 2000; Craik et al., 1999; Farrow et al., 2001; Fletcher et al., 1995; Gallagher et al., 2000; Goel et al., 1995; Vogeley et al., 2001; Zysset et al., 2002, 2003). It may be noteworthy, however, that in the studies on the Theory of Mind, there was a tendency of the activation peak to be located more anteroventrally when the tasks required story comprehension (Brunet et al., 2000; Fletcher et al., 1995; Gallagher et al., 2000; Vogeley et al., 2001) and more posterodorsally when the tasks did not (Castelli et al., 2000; Gallagher et al., 2000; Goel et al., 1995). Although we can neither extract advanced interpretation in the

function of anterodorsal subdivision from the results of our study nor from those of others, it is obvious that detailed conceptualization of the social inference, including the interaction with tasks, is required to clarify the functional anatomy of the medial prefrontal cortex.

Some methodological considerations may be required. One may criticize the lack of validation procedure in our self-evaluative questionnaire and may suggest adoption of established questionnaires. However, we consider this not the case. We intended to extract independent factors in data from a specific set of samples (the subjects and the target persons), that is, separating one factor from others; one cannot expect this independency or orthogonality of measures from a combination of established questionnaires. Questionnaires for general use are validated in terms of stability across populations and against the interaction with other factors, which may be preferable but not necessary in this study. Concerning the interpretation of the second PC, one may suspect the factors that are orthogonal to the emotional valence in some cognitive models of emotion (Davidson, 1992; Osgood et al., 1957; Russell, 1980; Schlosberg, 1954) of an alternative interpretation. We consider it unlikely because many items that evaluate the emotional state except for those related to the amount of episodic memory have small loadings to the second PC. We do not argue, however, that we should forget about the relationship between the second PC and emotion. We rather consider that we should be aware that the value information or "summary knowledge" of personal disposition partly shares properties with emotion, in that both are intuitive, automatic, or nonverbal, for advanced conceptualization in the future. Although several comprehensive theories on such aspects of human behavior have recently been proposed in the field of cognitive neuroscience (Brothers, 1997; Damasio, 1994), it appears that a more pragmatic conceptualization is still awaited. Upon consideration on these issues, we consider it appropriate to state simply that the second PC is independent of emotional valence and is strongly related to the amount of episodic memory.

Conclusion

A significant target dependency in activation was observed in the posterodorsal, polar, and ventral subdivisions of the medial prefrontal cortex, the right orbitoinsular junction, the left temporal pole, the left superior temporal sulcus, the cerebellum, and the thalamus, confirming the existence of target dependency in activation during the dispositional inference. PCA of the data from the self-evaluative questionnaire provided two independent factors. The amount of episodic memory appeared to be measured as a principal component score for the second PC, which was independent of the emotional valence. The measure was positively correlated with the activation in the polar subdivision of the medial prefrontal cortex, and negatively with that in a region in the left superior temporal sulcus. According to a recent cognitive model of dispositional inference and together with available knowledge about the functional roles of these two regions, the results suggest that these two regions play roles supplementary to each other in dispositional inference: the region in the superior temporal sulcus in the processing of relevant episodic exemplar and the polar subdivision of the medial prefrontal cortex in the processing of summarized value information about the target person.

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