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How is Social Functioning of Schizophrenics Measured?

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Measuring social functioning of schizophrenics is becoming an important clinical issue in the era of community care, where persons with mental illness can live in the community. Neuro- and social-cognitive function studies on the outcome of schizophrenia focus on researching brain functioning, and social functioning is a co-primary outcome measure of intervention. In this review, the viewpoint of measuring social functioning is clarified, typical and recommended assessment scales are introduced, methods to be developed for measurement are discussed, and how to measure social functioning in clinical and research settings is summarized. The axes of classifying measures include functional capacity/real-world functioning, subjective/objective evaluation, and rating/observing behaviors. Six social functioning scales were chosen as recommended scales in the study of real-world functioning as a co-primary measure in NEMH-MATRICS. Almost all scales are objective rating with the interviewing of informants. The functional capacity or competence is evaluated in performance tasks. While the scale of processing tasks of everyday functioning (UPSA) was recommended in many studies, there is no standard for assessing social skills or social problem-solving skills, because these skills differ greatly depending on the sex, age, and culture. Intervening variables among neuro/social cognitive functioning, functional capacity, and real-world functioning are intrinsic motivation, meta-cognition, self-efficacy, expected support, and the environment and support which might decrease the association of basic cognition and the functional outcome. In a clinical setting, these intervening variables, hope and subjective evaluation of support needs, and life history regarding the previous capacity are needed as well as assessment scales to develop a plan for intervention. Objective assessment scales are useful for measuring the effects of intervention.

＜Author's abstract＞

＜**Key words**：social functioning, schizophrenia, real-world functioning, functional capacity, performance test＞

精神病発症危険状態への薬物療法について

根本　隆洋*　水野　雅文*

抄録：精神病発症危険状態（ARMS）は予防医学的観点において画期的で重要な概念であると思われる。しかしその特性ゆえに介入のあり方については様々な議論があり，抗精神病薬の投与の是非は特に難題であるといえる。発症予防効果という点からは，服薬中における発症の遅延効果にとどまるようで，結局いつまで予防的投与を続ければよいのかというジレンマにはまりこんでしまう。現時点では，発症予防を目的とした積極的な抗精神病薬の投与に対するコンセンサスは得られていないと考えられる。一方で，ARMSの微弱な精神病症状への対症療法としての効果は期待できるものの，その適応は例外的な場合に限り，まずは認知行動療法などの非薬物療法により軽減を試みることが原則となるであろう。科学的不確実性やリスクに常に留意しながら疾患早期段階の診療に臨むことが必要である。
精神科治療学　28(7)：901-908，2013

Key words：*at-risk mental state, early intervention, pharmacotherapy, prodrome, schizophrenia*

Ⅰ．はじめに

本特集のテーマは「軽症例に対する精神科薬物療法のあり方」であるが，その中で精神病発症危険状態（at-risk mental state：ARMS）を扱うことには議論を伴うかもしれない。ARMSとは統合失調症のみならず感情精神病（精神病症状を伴う気分障害）なども含めた「精神病」の発症リスクの高い状態を指すが，その概念の形成過程からは，やはり統合失調症の発症リスクを主眼に置いているといえる。それではARMSが軽症の統合失調症かというと，全くそのような概念ではない。軽微な精神病症状を呈するものの統合失調症の診断基準を満たさず，いずれ統合失調症に移行するかといえば必ずしもそうではなく，むしろ多くは移行しないという，一見捉えどころのないような状態であるが，早期介入の視点に立てば画期的で極めて重要な概念であると思われる。しかしその特性ゆえに，早期発見はおろか早期治療に至っては様々な議論があり克服すべき課題も山積している。それでも同領域が精神医学の一大潮流となっているのは，個のレベルおよび社会のレベルにおいて予防精神医学に多大な期待と要請があるからに違いない。本稿では，統合失調症における早期介入の重要性とともに，その推進に際して検討すべき課題，そして最も難題であるARMSにおける薬物療法のあり方，特に抗精神病薬の投与について考えてみたい。

Pharmacological treatment in patients with an at-risk mental state for psychosis.

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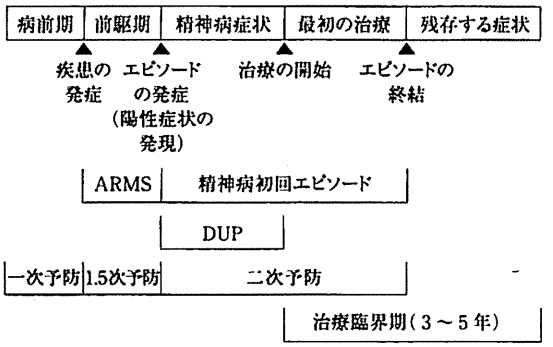

図1　統合失調症の早期段階
ARMS : At-Risk Mental State
DUP : Duration of Untreated Psychosis

Ⅱ．統合失調症の早期介入

統合失調症の早期介入，すなわち早期発見と早期治療の試みがこの15年間ほど非常に注目を集め，精神医学における主要テーマの1つとなっている。かつての長期入院主体の医療から包括的な地域ケアへの移行により，患者の社会生活における機能や生活の質は明らかに向上したと考えられる。ただ一方で，適切なケアやサポートの実施にもかかわらず，患者の機能障害の回復に多くの制限がみられるのも事実であった。疾患がすでに慢性化した時期における機能の回復の困難さに改めて直面化する中，疾患の予後を改善する取り組みとして早期介入への期待が高まっていった。早期に発見し早期に適切に治療すれば良好な予後が期待できるという，医療において自明のことである。

統合失調症の早期段階として，発症間もない初回エピソードに関心が向かい，精神病未治療期間（duration of untreated psychosis : DUP）の長短が重要な予後決定因子であること，すなわちDUPが短いほど転帰が良好であることが明らかにされた。さらに，発症後3～5年間が治療の成否を分け長期予後を左右する「治療臨界期（critical period）」であると考えられるようになった（図1）。この期間内に精神症状や社会機能の悪化，再発や自殺の問題，薬剤治療抵抗性の形成が高率にみられ，その期間を過ぎてしまうと概ねその水準で固定してしまうのである。治療臨界期を逸してしまうと治療の効果は大きく減弱するといえ，DUP短縮への取り組みはこの治療臨界期における治療開始に直結している[13]。

Ⅲ．統合失調症の前駆期

統合失調症の早期段階への関心は良好な長期的転帰の達成にとどまらず，発症自体の頓挫を目指して，閾値下の精神病状態にある「前駆期」へとさらに遡っていった。統合失調症においては，幻覚や妄想などの明らかな精神病エピソードを呈する以前から，さまざまな主観的もしくは客観的な変化が生じていることが知られていた。前駆期において，その前半では抑うつ気分，不安，不眠，刺激性，ひきこもり，薬物乱用などの精神症状や行動変化が現れるが，いずれも他の精神障害においてもみられる非特異的な症状や徴候であり，これらの出現をもって統合失調症の前駆期を同定することは困難である。そこで，前駆期の症状に関する諸研究をもとに再検討が行われ，前駆期の後半においては微弱ながらも特徴的な精神病症状がみられることが見出だされた。そして，症状の強度，頻度，持続期間に基づき，近い将来（1年以内）に精神病を発症するリスクの高い3つの状態が同定された（表1）。さらに，より高い精度と信頼性をもって前駆期を前方視的に診断していくためにComprehensive Assessment of At Risk Mental States（CAARMS）やStructured Interview for Prodromal Symptoms/Scales of Prodromal Symptoms（SIPS/SOPS）などの，前駆状態のための操作的な包括的診断基準が開発された[9]。

ところで，「前駆期」とは明確な発症がみられたのちに「あの時期が前駆期だったのだ」と振り返るような後方視的な概念であるため，早期発見と早期治療を目的とした研究および臨床実践の上では，「発症するとは断言できないが，発症のリスクが非常に高まっている」と前方視的に評価する必要があり，「前駆期」との表現を用いず，精神病発症危険状態として診断される。これまでの報告では，1年間にARMSの10～40%が精神病

表1　精神病発症のハイリスク状態

短期間の間歇的な精神病状態 Brief Intermittent Psychotic State (BIPS)	通常の精神病の診断基準には該当しないような，短期間に限定された精神病レベルの陽性症状が，最近みられるようになった状態
微弱な陽性症状 Attenuated Positive Symptom State (APS)	妄想には至らない程度の奇異な思考，幻覚には至らない程度の知覚の異常，思考障害と呼ぶには十分ではない程度のまとまりのない発話などがみられる状態（中等度以上だが精神病レベル未満の陽性症状を認める）
遺伝的リスクと機能低下 Genetic Risk and Deterioration State (GRD)	精神病の遺伝的リスク（第1親等家族に統合失調症スペクトラム障害を認めるか，本人に失調型パーソナリティ障害を認める場合）と，社会的職業的能力の低下（最近1年間にGAFスコアが30%以上低下し，その状態が最近少なくとも1ヵ月間持続している）の併存した状態

に移行するとされ，適切な介入によって発症を遅らせたり頓挫させたりすることが期待されている。前駆期が始まってから顕在発症に至るまでの時間は，平均4.8年といわれ，前駆期にはすでに認知機能や社会機能の低下が生じているとの報告，それを裏付けるかのように進行性脳病態が前駆期から生じていることを示す研究もみられる。

Ⅳ．ARMSの診断に伴う問題

ARMS患者への関わりにおいては格別な倫理的および心理的配慮を要することは，誰にも容易に予想されるであろう。特に「偽陽性」の問題，すなわち前述した操作的診断基準を用いてARMSと診断された場合でも，精神病に発展する者は多くとも40%程度にとどまり，このような人たちも含む一群への介入の是非も問われている。一方，偽陽性の中には，適切な介入をされたことにより本来起こりうるはずの発症を回避できた「偽偽陽性」と呼ぶべき症例も当然含まれることになる。このように，ARMSの診断には複数の問題が内在している。また，その結果をどのように本人や家族に伝えるかも容易ではない。

Ⅴ．ARMSに対する治療

ARMSの診断における偽陽性の存在の問題は，ARMSにおける治療の是非にもつながっている。しかし，自覚的もしくは客観的な不調や困難により本人や家族が援助を求めてわれわれ医療者の前にやって来た際には，その困難や苦痛に焦点を当てた適切な治療を行うことに異論はないであろう。McGorryらは，精神病の各ステージに応じた発見的方法と安全かつ効果的な介入方法を示した臨床病期分類（clinical staging）[11,12]を提案し，病態の進行を阻止するための治療戦略を明確にしている（表2）。ARMSの時期に積極的な介入を行うことは，不適切な行動の形成や社会的なひきこもりを軽減するなど社会機能や精神機能の低下を防ぎ，そして自尊心や自己効力感の維持にも貢献すると考えられる。

非特異的な症状が主体の前駆期の前半においては心理的な配慮とアプローチが重要である。前駆症状を呈する者の多くは思春期もしくは青年期にあり，正常な心理発達の過程における問題を抱えながら，その上に前駆期に伴うさまざまな不安や心配事が重畳したり複合したりしている。思春期・青年期心性を理解し配慮しながら，前駆期の症状や問題を取り扱っていくことが重要である。症状への対処方法や具体的な問題解決，ストレスマネジメントなどの認知行動療法（cognitive behavior therapy：CBT）的アプローチが有効であることも報告されている。ARMSに対するCBTにおいては，精神病症状の発症モデルに基づいた認知的な概念図を用いながら，精神病性の症状とともに主観的な苦痛や悩みにも焦点を当て，患者に合わせて臨機応変に治療的共同作業を進め問題を解決していくことが重要とされる[7]。

表2　精神病の臨床病期分類（clinical staging）（文献12を引用改変）

臨床病期	定義	対象	効果が期待される介入方法
0	精神病状態ないし重篤な気分障害の危険が増大している。 精神病症状はない。	1親等に遺伝負因のある10代の若者	精神保健や家族心理教育，薬物療法，短期認知技能訓練などに関する知識の普及・啓発活動
1a	精神病状態ないし重篤な気分障害の軽度または非特異的症状。 認知機能症状を含む。 軽度な機能障害や機能低下。	10代人口のスクリーニング，かかりつけ医やスクールカウンセラーからの紹介があった10代のスクリーニング	メンタルヘルスの知識教育，家族心理教育，CBT，積極的な物質乱用予防対策の実施
1b	超危険状態（Ultra High Risk）：中程度だが閾値下の症状。中程度の認知機能障害や事例性直前の機能低下（GAF<70）。	教育機関やかかりつけ医，救急部や福祉関連施設からの紹介	家族心理教育，CBT，積極的な物質乱用予防対策の実施，非定型抗精神病薬の投与や抗うつ薬や気分安定薬
2	精神病状態ないし重篤な気分障害の初回エピソード 中等度-重度の症状を呈し，認知機能障害や機能低下を呈し，閾値を完全に越えている（GAF30～50）	かかりつけ医，救急部や福祉施設，精神科クリニック，薬物物質乱用治療施設からの紹介	家族心理教育，CBT，積極的な物質乱用予防対策の実施，非定型抗精神病薬や抗うつ薬や気分安定薬，職業リハビリテーション
3a	初回エピソードからの不完全寛解 病期4への連続がうかがわれたり移行する可能性がある。	かかりつけ医または専門医療サービス	病期2と同様であることに加え，完全寛解を目指した医学的あるいは心理社会的戦略に重点を置く
3b	精神病状態ないし気分障害の再発と再燃。これらは治療により初回エピソードから寛解までの間に到達した最善の水準より低いGAFや残遺症状，認知機能の水準で安定する。	かかりつけ医または専門医療サービス	病期3aと同様であることに加え，再発予防と“早期警告サイン”戦略
3c	臨床症状の拡大を伴う多数回の再発。疾患の影響が明らかに存在。	専門医療サービス	病期3bと同様であることに加え，長期の安定を強調すること
4	重篤かつ遷延性あるいは寛解しない疾患。症状，認知機能，障害の各診断基準に照らして判断すること。 注意：特定の臨床的基準あるいは機能的基準（病期2から）から，あるいは治療への反応性不全（病期3aから）により，初回診察時点から直接この病期へ向かうこともある。	専門的治療	病期3cと同様であることに加え，clozapineはじめ他の第3世代薬剤処方の可能性の検討，障害が併存する中での社会参加の推進

Ⅵ．ARMSに対する抗精神病薬の投与について

微弱な精神病症状が明らかに存在し，精神病エピソードへの進展が切迫しているような前駆期の後半においては，抗精神病薬の投与も現実的に治療の選択肢に挙がってくるかもしれない。ARMSに対する抗精神病薬の有効性を検証した研究を振り返ってみたい。

ARMSを対象とした最初のRCTが2002年に豪州のMcGorryらにより発表された[10]。ケースマネジメントや症状モニタリングなども含む包括的な支持的精神療法による通常治療群（n＝28）と，それらに加えて少量1～2mg（平均1.3mg）のrisperidone投与とCBTを実施した特異的治療群（n＝31）とで6ヵ月間の介入を行ったところ，通常治療群では10例（36%）で精神病への移行がみられたのに対して，特異的治療群では3例（10%）にとどまり，統計学的に有意な差が認められた。しかし，その後両群において通常治療のみを継続しさらに6ヵ月間追跡したところ，特異的治療群から新たに3例の移行者が現れ，研究開始12ヵ月後の時点においては，もはや移行率に差はみられなくなった。一方で，特異的治療群を服薬アドヒアランスによって詳細に検討すると，新たな発症例はいずれもアドヒアランス不良例であり，服薬アドヒアランス良好例に限れば通常治療群に比べて12ヵ月時点で有意に精神病への移行率が低かった。精神症状の改善については通常治療

群と特異的治療群の両方において全般的な改善を認め，群間の有意な差はなかった。

さらに，Phillipsらによって本研究対象者の中期的転帰に関する追跡調査が行われた[14]。約7割（通常治療群17名，特異的治療群24名）の患者で研究開始から3～4年時の追跡が可能であった（研究グループによるその間の介入はなされていない）が，その間に通常治療群では2例，特異的治療群では4例の移行者が現れ，中期的に移行率に差を認めない結果となった。短期的（12ヵ月）転帰の解析時と同様に，特異的治療群をアドヒアランスで分けた上での検討（アドヒアランス良好11例，不良13例）もなされたが，有意な差はみられなかった。

以上の結果から，服薬を継続していれば発症を先延ばしできるが服薬をやめてしまうと発症してしまう，すなわち発症自体の頓挫は容易ではないものの，抗精神病薬が発症の遅延には寄与する可能性が示唆された。しかしCBT併用の介入デザインであったため薬物療法単体の効果には言及できない。

米国におけるPrevention through Risk Identification, Management, and Education（PRIME）研究では，5～15mgのolanzapine服用群（31例）とプラセボ群（29例）とを比較するランダム化二重盲検が実施された[8]。1年間の治療期間と，さらに1年間の追跡期間が設けられた。Olanzapine服用群では治療期間内に5例（16%）が精神病に移行し，その後の追跡期間内にさらに3例が移行し，合計8例（26%）が精神病に移行したのに対して，プラセボ群では治療期間中に11例（38%），追跡期間に2例，合計13例（45%）が精神病に移行した。Olanzapine群の移行率が低かったものの，統計学的に有意な差には至らなかった。症状や機能レベルの変化においても，治療期間の前半においてはolanzapineの有意な陽性症状軽減効果を認めたものの，最終的に有意な差には至らなかった。薬物療法の副作用については，体重増加（olanzapine群で8.8kg，プラセボ群で0.3kgの増加）や疲労感（olanzapine群29%，プラセボ群3%）で有意な群間差を認めた。本研究から，薬物療法による一定の発症遅延効果や陽性症状改善効果が期待されるものの，副作用の発現を超えるベネフィットがあるかについては議論を伴うであろう。

Cornblattらは米国におけるnaturalistic studyにおいて，少なくとも8週間以上の薬物療法を受け半年以上の追跡を行えたARMS患者48名を対象に解析を行った（平均追跡期間は30ヵ月で，最長期間は60ヵ月）[2]。うち20例は抗精神病薬の処方はなく抗うつ薬が処方されていた（抗うつ薬群）。残りの28例は新規抗精神病薬が処方され，抗うつ薬が併用された例も含まれた（抗精神病薬群）。抗精神病薬群で43%（12/28）が精神病に移行したのに対して，抗うつ薬群では移行例は認められず，統計学的にも有意な差であった。ベースラインにおける重症度の違いに起因したのではないかと考えられたが，解体思考以外は両群に有意な差は認められなかった。一方，アドヒアランスの差は明らかで，抗精神病薬群では61%がアドヒアランス不良例であったのに対して，抗うつ薬群では20%にとどまり統計学的に有意であった。抗精神病薬群における発症12例のうち11例はアドヒアランス不良例であった。本研究の結果を受けて，英国のOutreach And Support In South London（OASIS）プロジェクトにおいても抗うつ薬の精神病予防効果に関するnaturalistic studyが行われたが，2年間のうちに抗精神病薬群では29%の移行であったのに対して，抗うつ薬群では8%にとどまった。しかし，治療の選択は十分な説明の上で患者により決定される研究デザインであった。これら2つの研究から，精神病移行予防に関する抗うつ薬の可能性が示されたものの，そもそも切迫していない比較的良好な経過が見込まれるような症例に抗うつ薬が選択されていたのではないかとも考えられ，抗うつ薬の効果については今後RCTが必要であると考えられる。

以上の研究が精神病への移行予防を主な目的としていたのに対して，移行のみにこだわらずむしろARMSにおける精神症状や機能障害の改善を主目的にした研究もみられる。

ドイツのGerman Research Network on Schizophrenia（GRNS）研究は，通常治療群と通常の治療にamisulprideを加えた群を12週間比較して，

両群において精神症状や機能障害の改善がみられたがamisulprideを加えた群のほうが有意に優っていたこと，しかしamisulprideを加えた群では体重増加の問題を伴ったことを報告している[15]。

米国のWoodsらは15人のハイリスク患者に対してaripiprazole（5～30mg）を用いた8週間のオープンラベル試験を行い，前駆症状の有意な改善と脱落率の低さ（13%）が報告されている[18]。しかし8例でアカシジアを認めた。本邦においてはKobayashiらがaripiprazoleを用いた8週間のオープンラベル試験を行い，前駆症状や全般的機能の改善と良好なアドヒアランスに加えて病識の改善効果を報告している[6]。またTsujinoらは52週にわたる介入研究においてperospironeの効果と安全性を報告している[17]。

Ⅶ．抗精神病薬投与の是非

薬物療法の是非の問題は，すなわちリスク・ベネフィット比の問題であり，特に従来型抗精神病薬においてはそのリスクとして非常に難治な遅発性ジスキネジアや致死性の悪性症候群，新規抗精神病薬においては体重増加や高血糖などの代謝系の副作用が高率に出現することが挙げられる。明確な精神病を発症するか否かわからぬような症例に対して，そのような薬剤を投与してもよいのかという倫理的問題がARMSの治療においては常に生じる。冒頭で触れたように，もしARMSが単に統合失調症の軽症例というのであれば，統合失調症という診断にすでに至っているがゆえに，ここまでの倫理的問題は生じないであろう。これらのリスクを凌ぐほどのベネフィットが明らかであれば受け容れられるのだろうが，発症予防という観点からは，服薬中は発症遅延効果が期待されるものの，服薬を終了してしまえば未服薬群と同じような転帰となってしまい，結局いつまで予防的投与を続ければよいのかというジレンマにはまりこんでしまう。また，抗精神病薬の投与によりドパミン受容体のup regulationが生じ，投薬の中止により発症のリスクがかえって高まってしまう懸念もある[3]。また，新規抗精神病薬の神経保護作用についての報告がみられる一方で，新規抗精神病薬も含めて薬剤暴露（用量および期間）に応じた脳体積の減少がみられるという報告もみられる[4]。現時点においては予防効果を目的として積極的に抗精神病薬を投与するというコンセンサスには至っていないと考えられる[5]。

一方で，発症予防ということではなく，いま目の前にある精神病症状に対する対症療法として，必要最低限の用量と期間に留めて細心の注意を払って投与することは，ある程度受け容れられやすくなるのではないか。辻野らによる処方意識調査の報告からは，本邦においてARMSに対して比較的少量であるものの抗精神病薬が多く処方されている現状が推察される[16]。しかし，ARMSの段階では精神病症状は微弱なものであるため，まずはCBTなど非薬物療法により軽減を試みるということが原則となるであろう。International Early Psychosis Association（IEPA）による早期精神病ガイドラインにおいては，ARMSに対する抗精神病薬の使用は例外的な場合に限られるとした上で，投与が考慮されうる場合として，①急速な悪化が生じている時，②重篤な自殺のリスクが存在するがいかなる抗うつ薬も無効である時，③攻撃性や敵意が増強し他者への危険性を有する時を挙げている[5]。投与にあたっては短期で低用量の新規抗精神病薬が推奨され，6週間後に効果が認められるならば，リスクとベネフィットを説明し患者の同意を得られた際は，その後6ヵ月から2年間投与が継続されるかもしれないと記されている。

海外における抗精神病薬の投与状況については，前述のPhillipsらによる中期的な転帰の報告において，発症者のうちで中等度の割合（特異的治療群であった者70%，通常治療群であった者28.6%）が，研究的介入から数年後の再評価までの間で抗精神病薬を投与されたことがあると報告しているのに対して，非発症者においては抗精神病薬が投与された者はほとんどいなかったようで，海外においてARMSへの抗精神病薬の処方は非常に少ない様子がみてとれる[14]。しかし非発症者における抗うつ薬もしくは抗不安薬の処方は高率（特異的治療群で70%，通常治療群で53.8%）であり，これらの薬剤の処方に対しては抗精神病薬ほどハードルが高くない様子がうかがわれる。

表3　NIMHによる早期介入における指針（文献1を引用改変）

1．無症状の人への抗精神病薬による治療は，臨床においても研究においても正当化されない。
2．評価者間信頼性が許容範囲であればARMSと診断できる。しかし誰が精神病性障害を発症するかについては予測不可能である。
3．ARMSの診断基準を満たした人が必然的に精神病に移行するわけではない。
4．精神病の診断基準を満たした人に対する最適な治療は確立されていない。したがって，すべての治療選択肢を提示するべきである。
5．ARMSの人の研究参加や治療にはリスクとベネフィットがある。リスクとして，発症するとは限らない疾患に対する脆弱性があると見なされること（不必要に不安になること，差別，自ら限界を課してしまうこと）や，治療を行う場合に薬剤によって望ましくない副作用が引き起こされる可能性があることなどが挙げられる。
6．25歳以下の人への抗精神病薬の使用については，まだ不明な点が数多くあることを文書に明記すべきである。潜在的なリスクとして，錐体外路症状，遅発性ジスキネジア，性機能障害，著しい体重増加，糖尿病や心血管疾患といった長期的な合併症などが挙げられる。
7．研究や治療に参加する主なベネフィットは，発症に対して早期に効果的な治療を受けることができること，治療によって前駆期もしくはARMSにおける症状自体の苦痛を緩和できることである。
8．前駆期の人が治療を受けるべき期間は不明であるため，決められた期間ごとに，コスト・ベネフィット比を含む治療の有用性について再検討すべきである。

Ⅷ．おわりに

米国のNational Institute of Mental Health (NIMH)は，患者および早期介入に携わる臨床医や研究者が十分に理解し心得ておくべき点を表3のように挙げている[1]。科学的不確実性やリスクを常に肝に銘じながら，謙虚に疾患早期段階の診療に臨む必要があろう。また，患者が有する権利として，必要な情報が得られること，治療へのアクセスが可能であること，そして治療を受ける自由と拒否する自由があること，すなわち「よい」治療を受ける権利と「悪い」治療を拒む権利，その自主的な判断をするための援助を求める権利を有していることに留意し，十分なインフォームド・コンセントを行うとともに，個々それぞれに最善の治療の選択と提供がなされるように，患者とその家族，そして様々な職種のプロフェッショナルを交えながらの的確なケースマネジメントを行うことが，結局のところ最も重要であると考えられる。

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Cerebral Cortex Advance Access published December 2, 2013

Cerebral Cortex
doi:10.1093/cercor/bht317

How Self-Determined Choice Facilitates Performance: A Key Role of the Ventromedial Prefrontal Cortex

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Recent studies have documented that self-determined choice does indeed enhance performance. However, the precise neural mechanisms underlying this effect are not well understood. We examined the neural correlates of the facilitative effects of self-determined choice using functional magnetic resonance imaging (fMRI). Participants played a game-like task involving a stopwatch with either a stopwatch they selected (self-determined-choice condition) or one they were assigned without choice (forced-choice condition). Our results showed that self-determined choice enhanced performance on the stopwatch task, despite the fact that the choices were clearly irrelevant to task difficulty. Neuroimaging results showed that failure feedback, compared with success feedback, elicited a drop in the vmPFC activation in the forced-choice condition, but not in the self-determined-choice condition, indicating that negative reward value associated with the failure feedback vanished in the self-determined-choice condition. Moreover, the vmPFC resilience to failure in the self-determined-choice condition was significantly correlated with the increased performance. Striatal responses to failure and success feedback were not modulated by the choice condition, indicating the dissociation between the vmPFC and striatal activation pattern. These findings suggest that the vmPFC plays a unique and critical role in the facilitative effects of self-determined choice on performance.

Keywords: autonomy, intrinsic motivation, orbitofrontal cortex, striatum, value representation

Introduction

Many believe that when people can make personal choices in accord with their interests and values they have both improved experience and performance. In accord with this view, psychological experiments have robustly revealed the advantage of self-determined choice: When participants could choose a task from multiple ones available in accord with their own interest or value (i.e., self-determined choice), their task performance were improved as compared to when they were assigned a task without choice (i.e., forced choice), even if task difficulty was not different (Patallet al. 2008; Leottiet al. 2010). The practical implications of this facilitative effect of self-determined choice cannot be overemphasized. In fact, the effect of self-determined choice has been investigated in a variety of areas, such as education (e.g., Cordova and Lepper 1996), organizations (e.g., Van den Broeck et al. 2008), and creativity (e.g., Amabile 1996). The beneficial effect of self-determined choice also has theoretical implications in a wide range of human models such as normative economic theories or reinforcement learning theory (Montague and Berns 2002), because these normative theories are basically indifferent to whether the choice was made out of one's own will (self-determined choice) or by others (i.e., forced choice).

Despite the broad significance, however, surprisingly little neuroscience research has been conducted to examine the neural mechanisms underlying the self-determined choice. In addition, the limited number of previous research has a restricted focus in two respects. First, previous research in neuroscience has not employed an achievement task (i.e., a task that involves one's skill and competence to obtain high performance) and, therefore, these studies did not address the possible performance enhancement in self-determined choice. For example, several researchers investigated the neural correlates of self-generated motor action (Haggard 2008; Passingham et al. 2010), but these studies focused primarily on identifying the brain areas that cause self-generated action of a simple motor task, and its resultant performance has never been questioned. One recent study investigated the neural responses to the anticipation of personal choice (Leotti and Delgado 2011), but this study used a pure probabilistic task and did not target the consequential performance caused by self-determined choice.

Second, these previous studies have focused only on the initiation of self-determined choice (Haggard 2008; Passingham et al. 2010) or the anticipation of self-determined choice (Leotti and Delgado 2011), but overlooked another important aspect of task engagement: Processing of outcome feedback. Outcome processing is one of the fundamental and key psychological processes underlying effective performance in achievement tasks (Carver and Scheier 1998; Kluger and DeNisi 1996). Accordingly, it is possible that self-determined choice modulates the neural activity during the outcome feedback period. In fact, a number of behavioral studies indicated that the psychological process of outcome feedback is one prominent factor underlying the facilitative effects of self-determined choice (e.g., Mikulincer 1988; Molleret al. 2006; see also Legault and Inzlicht 2013, for a study using electroencephalogram).

Thus, the goal of the current study is to examine the neural correlates of the beneficial effects of self-determined choice on task performance, especially focusing on the outcome feedback period. Two primary brain regions have been implicated in processing outcome feedback for an achievement task (Tricomi et al. 2006; Daniel and Pollmann 2010; Murayama et al. 2010; Shohamy 2011)—the striatum and the ventromedial prefrontal

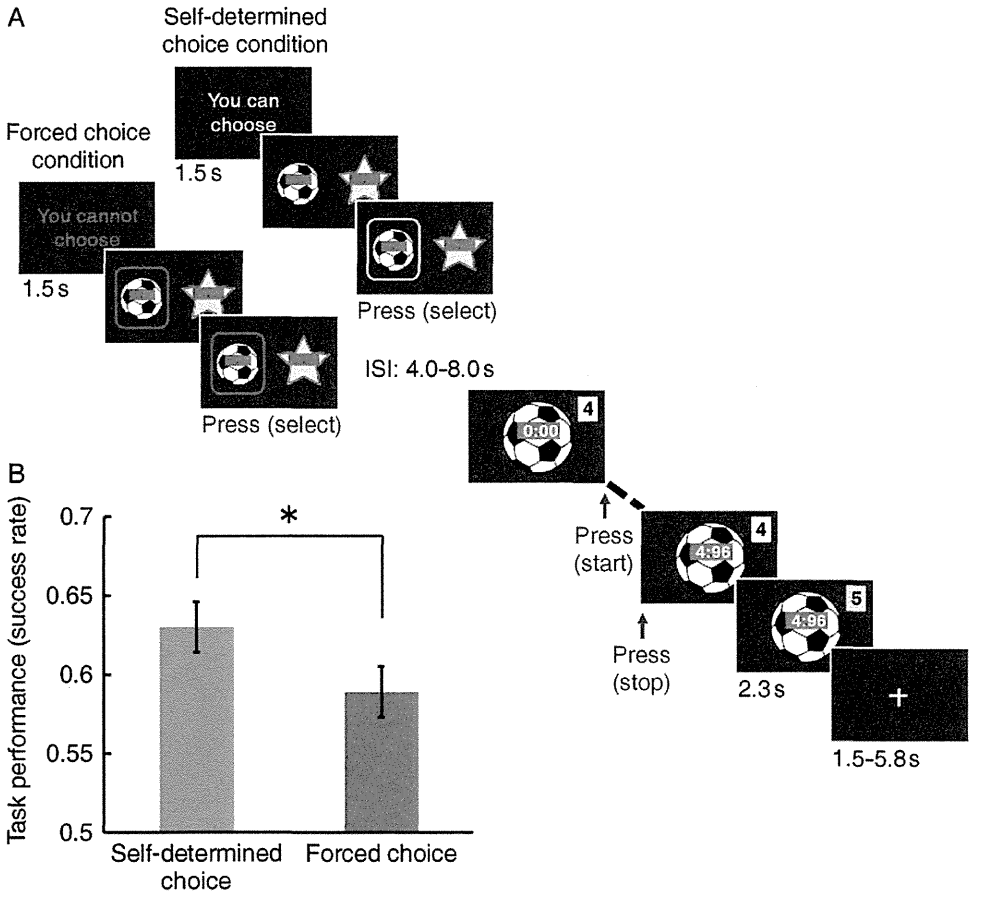


Figure 1. Experimental procedure, materials, and behavioral results. (*A*) Depiction of the experimental procedure. (*B*) Means and standard errors of the performance of the stopwatch task (success rate). Self-determined-choice condition significantly enhanced task performance in comparison to forced-choice condition ($t_{30} = 2.49$, $P = 0.018$).

cortex (vmPFC). Previous studies have indicated the flexible role of both the striatum and the vmPFC (and the adjacent subgenual anterior cingulate cortex, ACC) in representing task values that are regulated by cognitive states and nuanced contexts (Coricelli et al. 2005; Fliessbach et al. 2007; Hare et al. 2008; Plassmann et al. 2008; De Martino et al. 2009; Weber et al. 2009). In fact, the value representation in the striatum and the vmPFC has been shown to be influenced by various factors, such as intertemporal choice (Kable and Glimcher 2007; Sellitto et al. 2010), social norms (Koenigs et al. 2007; Izuma et al. 2008), and emotion regulation (Delgado et al. 2008; Wageret al. 2008). Accordingly, we expect that the effect of self-determined choice would manifest as brain activity change in the striatum and/or the vmPFC in response to outcome feedback.

In this study, participants played a stopwatch game (Murayama et al. 2010) where the goal was to press a button to stop a stopwatch within a specific time window. On each trial (Fig. 1*A*), participants were presented with a pair of stopwatches, and they were told they could freely choose the one they wished to use in the 'self-determined-choice condition'. In the 'forced-choice condition', they were told to play with a stopwatch that was assigned by a computer. After a stopwatch was selected, it appeared in the center of the screen. Then participants played the stopwatch task and received feedback. Using functional magnetic resonance imaging (fMRI), we investigated how self-determined choice modulates the activation of the striatum and vmPFC in responses to outcome feedback in the stopwatch task.

Materials and Methods

Participants

A total of 35 healthy participants were recruited from Tamagawa University (Tokyo, Japan). One participant could not finish the experiment; 3 indicated they were distracted and did not follow instructions (in fact, more than 60% of the total error trials were produced by these participants). Accordingly, these 4 participants were excluded prior to fMRI data analysis, resulting in the final sample of 31 [mean age = 20.7 (SD = 2.4), 14 males and 17 females]. All participants gave informed consent for the study and the protocol was approved by the Ethics Committee of Tamagawa University. Four of the 31 participants took part in the experiment without fMRI scanning. These participants were included only in behavioral results.

Experimental Tasks and Procedure

We used a stopwatch task that has been proven to be a useful achievement task in fMRI experiments (Murayama et al. 2010). In this task, participants were presented with a stopwatch, and the goal was to press a button with the right thumb so that the button press fell within 50 ms of the 5-s time point. This time window was the same across the participants. A series of pilot studies were conducted to determine the time window (i.e., difficulty) of the task so that participants could succeed on approximately half of the trials. We took this procedure because 1) previous literature indicated that people obtain the greatest

sense of achievement for the tasks of intermediate difficulty (Atkinson 1957), and 2) this rate of success allows a sufficient number of success or failure trials to be obtained for proper fMRI statistical analysis.

The experiment was composed of 3 scanning sessions, each session consisting of 36 main trials (~14 min each). In addition, 3 catch trials were included at the beginning of the experiment. Each trial (see Fig. 1A) started with a task cue (1500 ms) signaling either the self-determined-choice or forced-choice condition, followed by a presentation of a pair of stopwatches. In the self-determined-choice condition, participants were able to freely choose one of the stopwatches to play in that trial by pressing 1 of the 2 buttons. In the forced-choice condition, a rounded rectangle that encloses one of the stopwatches appeared 800–1200 ms (pseudorandomized) after the stimuli presentation, and participants had to select that stopwatch by pressing the corresponding button. In this condition, responses were not allowed until a rounded rectangle suggested one of the stopwatches. This procedure was intended to expose participants to the choice options almost equally in both self-determined-choice and forced-choice conditions. As a result, reaction time to make a choice (counting from the moment of stimuli presentation) was not statistically different between these 2 conditions ($M = 1443.0$ ms across the conditions). A trial-based linear mixed-effects modeling (Baayen et al. 2008) did not find a significant relationship between the reaction time to make a choice and task performance ($P = 0.46$). On making a choice, the stopwatch that participants had just selected appeared in the center of the screen, where participants could start playing the stopwatch task by pressing a button. When a stopwatch was displayed, the participant's total score was also displayed in the upper-right corner of the display area. A point was added to his or her score (800 ms after the button press) and the updated score panel flashed for 1,500 ms; no point was added when they failed. The points accumulated throughout the experimental session, but no tangible reward such as money was associated with success. Critically, the difficulty of all the stopwatches was identical—they were different only in their appearance. Participants were explicitly instructed about this fact.

An error message was presented when 1) participants pressed the button before a suggested choice was presented, 2) participants selected a stopwatch that was not suggested, 3) participants had not pressed the button 10 000 ms after choice options were presented, 4) participants had not pressed the button 10 000 ms after the chosen stopwatch was ready to start, or 5) participants had not pressed the button 8 s after the stopwatch started. In those cases, the same trial started again.

We randomly intermixed the self-determined-choice trials (36 trials) and forced-choice trials (72 trials) for each participant (details about the trial numbers will be described later) with the constraint that there were no more than 3 successive trials of the same condition. The intertrial interval (ITI) was jittered between 1500 and 5800 ms (average = 3500 ms). In addition to the ITI, after participants made a choice (both in the self-determined-choice and forced-choice conditions), there followed a variable interval between 4000 and 8000 ms (average = 6000 ms), after which participants could start the stopwatch by pressing a button. This variable interval allowed us to efficiently separate the choice-evoked brain activation from the activity associated with the initiation of the stopwatch task. The stimulus presentation and response recording were controlled by Cogent 2000 (http://www.vislab.ucl.ac.uk/cogent.php) running on Matlab. The instruction was provided through a computer program to prevent possible experimenter bias, and participants were thoroughly trained in advance to familiarize them with the task sequence.

After the last scanning session, participants were asked to indicate whether they enjoyed self-determined-choice or forced-choice trials (You had 2 types of trials, one where you could determine which stopwatch to play with, and the other where you were asked to choose a specific stopwatch to play with. Which trials did you enjoy more?).

Trial Matching

We prepared a total of 9 moderately attractive stopwatches from a larger set of stimuli (see Fig. 2). We presented all the possible pairs of different stopwatches 3 times to every participant (i.e., 108 main trials in total with 36 pairs)—one trial per pair of options when the participants were making self-determined choices and 2 trials per pair of options when the participants were making forced choices. In the 2 forced-choice trials within a pair, the experimental program made a different choice. With this procedure, it is assured for every participant that each of the self-determined-choice trials has a corresponding forced-choice trial that selected the same stopwatch from the same pair (forced-choice-matching trials). Importantly, in order to match self-determined-choice and forced-choice conditions as close as possible, unless otherwise noted, our statistical analysis included only the forced-choice matching trials (a within-participant yoked-control design; Peele et al. 1984). This way, we could compare the self-determined-choice condition and forced-choice condition with the identical pairs and choices within participants, achieving a perfect control for any confounding effects. Conceptually, forced-choice matching trials represent the situation where participants were externally forced to play with the stopwatch they like, which provides comparison without the confounding influence of differential emotional commitment to the task. Nonetheless, analyses focusing on forced-choice trials involving a different stopwatch (forced-choice nonmatching trials) will be also reported.

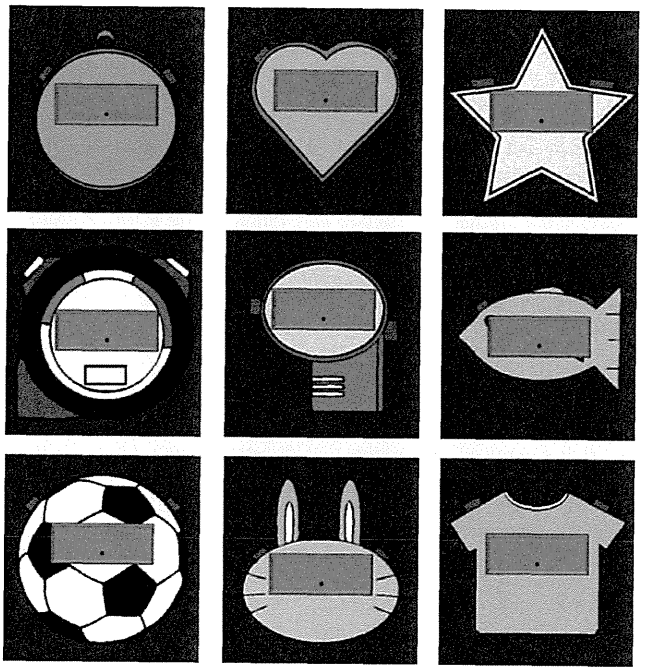


Figure 2. Nine types of stopwatches used in the current experiment. They are different in their appearance, but the difficulty of the task was identical.

fMRI Data Acquisition

The functional imaging was conducted using a 3-Tesla Siemens Trio A Tim MRI scanner to acquire gradient echo T_2*-weighted echo-planar images (EPI) with blood oxygen level–dependent (BOLD) contrast. Forty-two contiguous interleaved transversal slices of EPI images were acquired in each volume, with a slice thickness of 3 mm and no gap (repetition time, 2500 ms; echo time, 25 ms; flip angle, 90°; field of view, 192 mm^2; matrix, 64 × 64). Slice orientation was tilted 0.30° from the AC-PC line. We discarded the first 3 images before data processing and statistical analysis to compensate for the T_1 saturation effects.

fMRI Data Analysis

Image analysis was performed using Statistical Parametric Mapping 8 (SPM8; http://www.fil.ion.ucl.ac.uk). Images were corrected for slice acquisition time within each volume, motion-corrected with realignment to the first volume, spatially normalized to the standard Montreal

Neurological Institute (MNI) EPI template, and spatially smoothed using a Gaussian kernel with a full width at half-maximum of 8 mm.

For each participant, the BOLD responses across the scanning sessions were modeled with a general linear model (GLM). The analysis was intended to model the following effects: Presentation of cue in the self-determined-choice condition, presentation of cue in the forced-choice condition, task initiation in the self-determined-choice condition (success and failure trials were combined), task initiation in the forced-choice condition (success and failure trials were combined), success feedback in the self-determined-choice condition, success feedback in the forced-choice condition, failure feedback in the self-determined-choice condition, and failure feedback in the forced-choice condition. The onset of task initiation was set 1000 ms before the button press, because previous studies showed that preparatory brain activity begins about 1000 ms before action takes place (Haggard 2008). It should be noted that, in the regressors of forced-choice condition in task initiation and feedback periods, we only included the trials that suggested the option that the participants selected in the corresponding self-determined-choice condition (i.e., forced-choice matching trials). As indicated earlier, this procedure allowed us to control for any confounding factors associated with stopwatch selection. Both for task initiation and feedback periods, forced-choice trials that suggested the other option (i.e., forced-choice nonmatching trials) were coded as separate regressors. Choice period (i.e., between presentation of choice options and button press to make a choice), motion parameters, error trials, and session effects were also modeled as regressors of no interest. All the regressors (except for the motion parameters and the session effects) were calculated using a box-car function convolved with a hemodynamic-response function. Estimates were corrected for temporal autocorrelation using a first-order autoregressive model. The obtained parameter estimates were then taken to the second level, and a random effects analysis was performed.

In an additional GLM that aimed to control for the total number of failure (or success) experiences that individuals had on each trial, we added the cumulative number of failure trials as a trial-specific parametric modulator to the failure-feedback periods. The cumulative number of failure trials was computed and included in the model separately for the self-determined-choice and forced-choice conditions.

Analysis for the cue presentation period was a region of interest (ROI) analysis focusing on the ACC, insular cortex, striatum/pallidum, and midbrain (for reasons, see Results), with a priori anatomical ROIs defined by using the WFU-Pickatlas SPM tool (Maldjian et al. 2003): Using the AAL atlas, the ACC ROI consisted of the bilateral anterior cingulum; The anterior insula ROI consisted of the bilateral insula; and the striatum/pallidum ROI consisted of the bilateral caudate, putamen, and pallidum. The midbrain ROI was defined by the Talairach Daemon database. A familywise error-corrected significance threshold of $P < 0.05$ ($k \geq 5$ voxels) within these ROIs were used (the reported significant voxels also survived at $P < 0.001$, uncorrected, $k \geq 30$ voxels).

Analysis for the feedback period (i.e., our main analysis) was also a ROI analysis focusing on the striatum and vmPFC, with a priori anatomical ROIs defined by using the WFU-Pickatlas SPM tool (Maldjian et al. 2003). The striatum ROI consisted of the bilateral caudate and putamen, and the vmPFC ROI consisted of the bilateral gyrus rectus and medial orbitofrontal gyrus in the AAL atlas. A familywise error-corrected significance threshold of $P < 0.05$ ($k \geq 5$ voxels) within these ROIs were used (the reported significant voxels also survived at $P < 0.001$, uncorrected, $k \geq 30$ voxels). A preliminary exploration of the data indicated that there is a strong outlier in vmPFC activation in response to feedback [more than 3.8SD outside the mean value. Grubb's test for outliers (Grubbs 1950) was significant, $P < 0.01$]. Accordingly, we excluded this participant from the vmPFC analysis.

To quantify the pattern of effects in the ROI analyses, we further conducted a series of post hoc analyses using a cross-validation leave-one-out procedure to avoid a nonindependence bias in the post hoc analyses. Specifically, we re-estimated our second-level analysis (i.e., 2 × 2 ANOVA, see results), always leaving out one subject. We selected the peak voxel within the ROI (i.e., striatum or vmPFC) in these cross-validation second-level analyses. From that new voxel we extracted the β value from the left-out subject and used these β values in the series of post hoc t-tests. This procedure is akin to an independent functional localizer, and ensures the independence of the post hoc analyses (Esterman et al. 2010; Gläscher et al. 2010). All the post hoc analyses were conducted with this procedure. The brain–behavior correlation analysis was also performed based on these extracted β values.

For task initiation period, an exploratory whole-brain analysis was conducted ($P < 0.001$, uncorrected, $k \geq 5$ voxels). Moreover, we ran additional GLM that added the response time to initiate the stopwatch as a trial-specific parametric modulator to explore how the response time is correlated with brain activation.

For exploratory purpose, we also conducted a within-subject functional connectivity analysis between choice period and feedback period. This exploratory analysis was conducted in order to examine which brain activation during the choice period is related to the modulation effect of the vmPFC activation observed during the feedback period. The procedure took the following steps. First, a new GLM design file was constructed where each individual trial of the feedback period was coded with a unique independent variable. This allowed us to estimate the trial-by-trial brain activation (i.e., β values) from a seed region during the feedback period (Rissman et al. 2004). Next, the extracted β values from a seed region (using individual peaks) were included in the main GLM as a trial-specific parametric modulator during cue period. The parametric modulators were included in the model separately for the self-determined-choice and forced-choice conditions and for the success and failure trials, resulting in 4 different parametric modulators. With this procedure, β values associated with each parametric modulator represent the association between the brain activation during the cue period and seed-region activation during the feedback period in respective conditions (self-determined-choice/success, self-determined-choice/failure, forced-choice/success, and forced-choice/failure). Finally, to investigate condition-dependent change in functional connectivity, second-level random-effects analysis (e.g., ANOVA) was performed.

Results

Behavioral Results

Our data revealed that performance on the stopwatch task was significantly better in self-determined-choice condition ($M = 0.63$, SD = 0.15, range = 0.33–0.92) than in forced-choice condition ($M = 0.59$, SD = 0.14, range = 0.31–0.89; $t_{30} = 2.49$, $P = 0.018$; Fig. 1*B*). This provides the evidence that self-determined choice indeed enhances task performance. This effect was not moderated by gender difference ($P = 0.23$). In addition, the analysis on the post-session question showed that participants preferred self-determined-choice trials (94%) to forced-choice trials (6%; binomial test; $P < 0.0001$), suggesting that participants were indeed motivated for the self-determined-choice trials over the forced-choice trials.

To further validate our findings, we conducted additional controlling analyses. First, a latent growth curve modeling of task performance trajectory (McArdle et al. 1990) indicated that there is a linear increasing trend in task performance over trials, perhaps due to a practice effect, Exp (B) = 1.003, $P < 0.05$ (note that quadratic effect was not statistically significant, $P = 0.31$). Accordingly, to address the possibility that this linear trend may have influenced our findings, we computed the mean position (range is 1–108 and smaller number indicates earlier presentation) of the self-determined choice and the corresponding forced-choice (matching) trials. If a specific experimental condition tends to be positioned later in trials, this condition should benefit the practice effect. The results showed that forced-choice matching trials were positioned slightly later (M = 56.0, SD = 30.2) than self-determined choice trials ($M = 54.5$, SD = 30.4), and this difference was not statistically significant, $t_{30} = 1.64$, $P = 0.11$, suggesting that the practice effect is unlikely to bias our findings.

Second, we examined whether the performance in forced-choice trials influenced the choice of the self-determined choice trials within the same pair of stopwatches. For example, within a given specific pair of stopwatches, participants may have had a tendency to choose the stopwatch that they succeeded with in an earlier trial. This could potentially bias the findings (although in this case performance in forced-choice condition should be higher than that in self-determined-choice condition). Accordingly, we compared the task performance of forced-choice matching trials that were presented before the corresponding self-determined choice trials ($M = 0.59$, SD = 0.49) and those presented after the self-determined choice trials ($M = 0.59$, SD = 0.49). No statistically significant difference in performance was observed, $t_{30} = 0.08$, $P = 0.94$, indicating that performance in forced-choice trials did not influence the choice in the corresponding self-determined choice trials.

Finally, in order to examine how our matching procedure affected our findings, we examined performance of the forced-choice nonmatching trials. Interestingly, the performance comparison between forced-choice matching trials (trials used in the main analysis; $M = 0.59$, SD = 0.14; range = 0.31–0.89) and forced-choice nonmatching trials ($M = 0.59$, SD = 0.16; range = 0.31–0.92) did not reveal significant difference, $t_{30} = 0.16$, $P = 0.87$, indicating that selection bias may not have big impact on our behavioral findings. Self-determined-choice condition still showed better performance than forced-choice condition even when we collapsed these 2 forced-choice trials, $t_{30} = 2.71$, $P < 0.01$. Taken together, the set of controlling analyses indicated that the facilitative effects of self-determined choice on task performance cannot be attributable to methodological artifacts.

On the other hand, self-determined choice did not seem to influence task initiation time (e.g., reaction time between the onset of the chosen stopwatch and the button press to start the stop watch). Indeed, there was no significant difference between the self-determined-choice condition ($M = 793$ ms, SD = 326 ms) and forced-choice condition ($M = 773$ ms, SD = 303 ms), $t_{30} = 0.98$, $P = 0.33$. A trial-based generalized linear mixed-effects modeling (Baayen et al. 2008) further revealed that the task initiation time was not related to task success of the same trial ($P = 0.54$) or the interaction between task success and choice condition ($P = 0.64$).

Brain Activation in Response to Task Anticipation

A recent study showed that anticipation of self-determined choice activates a variety of brain regions, especially, the ACC, insula, striatum, and midbrain (Leotti and Delgado 2011). To confirm the validity of our experimental task for examining self-determined choice, we preliminarily investigated whether the self-determined-choice cue in our task (in comparison to the forced-choice cue) indeed activated those brain regions. We anatomically defined the ACC, insula, striatum/pallidum, and midbrain as ROI, and compared brain activation in response to the self-determined-choice cue with the forced-choice cue within these ROIs (see Fig. 3*A*; for completeness, Table 1 lists all regions displaying a significant effect in a whole-brain analysis). Because the cue was presented before the presentation of choice options (i.e., before the choice was suggested), all the forced-choice trials were included in the analysis. Consistent with the past study, the self-determined-choice cue activated the dorsal ACC (extending into the medial prefrontal cortex and

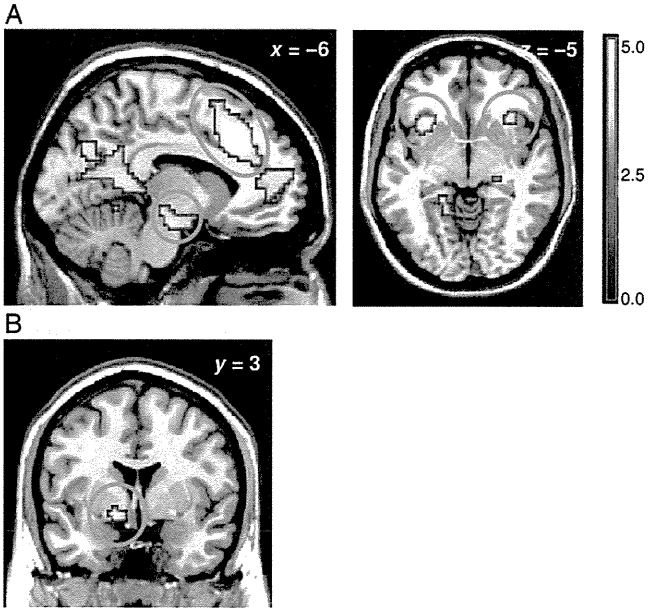


Figure 3. (*A*) Anterior cingulate cortex (left panel, upper circle), midbrain (left panel, bottom circle), and bilateral insula (right panel) activation elicited by self-determined-choice trials relative to forced-choice trials when participants were presented a task cue ($P < 0.05$, familywise error corrected; the image is shown at $P < 0.001$, uncorrected). Neural responses are displayed in sagittal and transaxial formats. (*B*) The ventral pallidum activation elicited by self-determined choice trials relative to forced choice trials when participants were presented a task cue ($P < 0.005$, uncorrected). Neural responses are displayed in coronal format.

Table 1
Effects of self-determined choice during cue presentation period

Region	Peak MNI coordinates			*t* value	*k*
	x	*y*	*z*		
Self-determined choice > forced choice					
L. Anterior cingulate cortex	−9	26	37	8.02	343
R. Anterior cingulate cortex	15	26	25	3.79	15
L. Medial prefrontal cortex	−9	56	13	4.35	223
R. Presupplementary motor area	12	14	67	3.87	14
L. Anterior insula	−33	17	−2	5.55	102
L. Anterior insula	−36	32	13	4.80	121
R. Anterior insula	36	23	−2	4.01	47
R/L. Midbrain	−9	−16	−17	4.86	97
R. Parahippocampal gyrus	27	−25	−17	5.22	103
L. Parahippocampal gyrus	−21	−25	−17	4.61	27
R. Isthmus	12	−43	10	4.75	42
L. Isthmus	−15	−43	4	4.66	51
R/L. Midcingulate cortex	−3	−4	31	4.00	58
L. Ventromedial prefrontal cortex	−9	29	−11	3.88	15
R. Superior frontal gyrus	12	14	67	3.70	11
R. Inferior frontal gyrus	48	8	25	4.28	37
L. Angular gyrus	−42	−64	46	3.60	7
R. Lateral prefrontal cortex	48	35	16	3.58	14
Forced choice > self-determined choice					
L. Supramarginal gyrus	−57	−46	40	4.80	61
L. Angular gyrus	−51	−55	28	4.45	57
L. Occipital cortex	−12	−100	16	4.21	53
R. Occipital cortex	12	−97	13	4.35	45
L. Supramarginal gyrus	−57	−25	22	3.66	10
L. Middle temporal gyrus	−54	−46	−5	3.77	10
L. Middle temporal gyrus	−54	−67	7	3.65	12
R. Fusiform gyrus	33	−73	−17	3.54	18
L. Cerebellum	−27	−79	−23	3.38	5

A whole-brain analysis results showing significant difference between the self-determined-choice condition and the forced-choice condition during the cue presentation period ($P < 0.001$, uncorrected, $k \geq 5$ voxels). *k*, number of significant voxels.

presupplementary motor area, pre-SMA), anterior insula, and midbrain more strongly than did the forced-choice cue ($P < 0.05$, family-wise error corrected). In the striatum, BOLD activity was greater when anticipating self-determined-choice relative to forced choice, but this difference was somewhat weaker and not statistically significant with family-wise error control. With a more lenient threshold used in the same previous study (Leotti and Delgado 2011; $P < 0.005$, uncorrected; Fig. 3*B*), however, the self-determined-choice cue did significantly increase activation in the ventral pallidum. In sum, these findings are consistent with previous work (Leotti and Delgado 2011) and support the validity of our experimental task for examining the neural correlates of the self-determined choice.

Brain Activation in Response to Outcome Feedback

Our primary interest was whether the brain activation in the striatum and vmPFC in response to outcome feedback would be modulated by the choice manipulation. Thus, we anatomically defined the striatum and vmPFC as ROIs, and conducted a 2 × 2 analysis of variance (ANOVA) with choice condition (self-determined choice or forced choice) and outcome feedback (success or failure) as factors within each ROI (for completeness, Table 2 lists all regions displaying a significant effect in a whole-brain ANOVA).

Table 2

Brain structures showing a significant effect in the 2 (choice condition; self-determined choice vs. forced choice) × 2 outcome feedback; success or failure) analysis of variance in response to feedback

Region	Peak MNI coordinates			*t* value	*k*
	x	*y*	*z*		
Success feedback > Failure feedback					
R. Ventral striatum	21	14	−5	4.99	299
L. Ventral striatum	−15	−1	−14	4.86	302
L. Occipital cortex	−45	−67	7	4.13	81
L. Dorsal prefrontal cortex	−18	32	61	4.05	56
L. Middle temporal gyrus	−57	−49	−8	3.76	17
R. Inferior temporal gyrus	45	−52	−14	3.61	15
R. Superior temporal gyrus	69	−31	7	3.60	5
L. Angular gyrus	−45	−70	34	3.62	35
L. Medial prefrontal cortex	−12	56	7	3.45	12
R. Primary motor cortex	30	−19	64	3.34	6
L. Precuneus	−3	−49	37	3.30	7
L. Inferior frontal gyrus	−48	5	25	3.23	5
Failure feedback > Success feedback		(No significant activation)			
Self-determined choice > forced choice		(No significant activation)			
Forced choice > self-determined choice		(No significant activation)			
Interaction					
R. Ventromedial prefrontal cortex	6	26	−14	3.96	32
L. Ventromedial prefrontal cortex	−12	32	−11	4.02	18
L. Ventromedial prefrontal cortex	−15	23	−20	3.72	10
R. Cerebellum	27	−70	−35	4.27	200
L. Cerebellum	−18	−55	−41	4.06	72
L. Cerebellum	−9	−55	−14	3.53	10
R. Anterior temporal cortex	48	−7	−23	4.07	25
R. Occipital cortex	27	−85	7	3.92	58
L. Occipital cortex	−30	−85	7	3.80	189
L. Posterior temporal cortex	−48	−43	1	3.72	20
R. Posterior temporal cortex	42	−55	1	3.61	8
R. Fusiform gyrus	30	−58	−11	3.88	22
R. Fusiform gyrus	42	−28	−14	3.43	6
L. Angular gyrus	−36	−67	31	3.41	12
L. Precuneus	−3	−58	31	3.31	8
L. Occipital cortex	−9	−70	25	3.30	5

A whole-brain analysis results showing a significant effect in the 2 (choice condition; self-determined choice vs. forced choice) × 2 outcome feedback; success or failure) analysis of variance in response to feedback ($P < 0.001$, uncorrected, $k \geq 5$ voxels). All the significant interactions have the same direction with the ventromedial prefrontal cortex as presented in Figure 5.

Activation in the striatum showed a significant main effect of outcome feedback ($P < 0.05$, familywise error corrected), indicating greater striatal activity in response to success (relative to failure) feedback. This is consistent with the previous findings that showed the striatum being sensitive to the valence of feedback even without any monetary incentives (Tricomi et al. 2006; Izuma et al. 2008; Murayama et al. 2010). However, no significant interaction was observed between choice condition and outcome feedback (Fig. 4). Indeed, the striatal activation in the self-determined-choice condition is not different from that in the forced-choice condition in response to either success or failure feedback (P's > 0.19); the greater activation in the striatum in response to success feedback (relative to failure feedback) was observed both in the self-determined-choice and forced-choice conditions (P's < 0.01).

In contrast, we found that self-determined choice modulated the brain activation in the vmPFC. Specifically, in the 2 × 2 ANOVA, the right vmPFC activation showed a significant interaction between choice condition and outcome feedback (Fig. 5; $P < 0.05$, familywise error corrected). Neither the main effect of choice condition nor outcome feedback revealed significant activation in the vmPFC. Post hoc analyses showed that, in response to success feedback, the vmPFC activation in the self-determined-choice condition was not different from that in the forced-choice condition ($F_{1,50} = 0.70$, $P = 0.41$). On the other hand, however, the self-determined-choice condition showed higher vmPFC activation in response to failure feedback than did the forced-choice condition ($F_{1,50} = 14.11$,

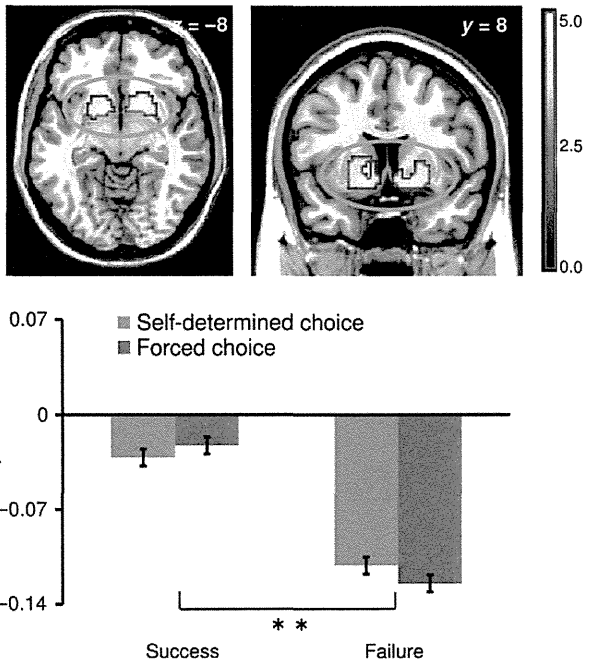


Figure 4. Bilateral striatum activation (peak at 21, 14, −5, and −12, 8, −8) showing a significant main effect of outcome feedback ($P < 0.05$, familywise error corrected; the image is shown at $P < 0.001$, uncorrected). Neural responses are displayed in transaxial and coronal formats. The bottom panel represents the mean β values (a 6-mm sphere centered on the peak) and corresponding SEs in the striatum as a function of choice condition (self-determined choice vs. forced choice) and outcome feedback (success vs. failure). Note that the graph plotted the activation in the right striatum to allow for reasonable comparison with Figure 5. The plot indicated that the striatum was strongly influenced by outcome feedback (positive vs. negative), but this effect was not modulated by choice condition.

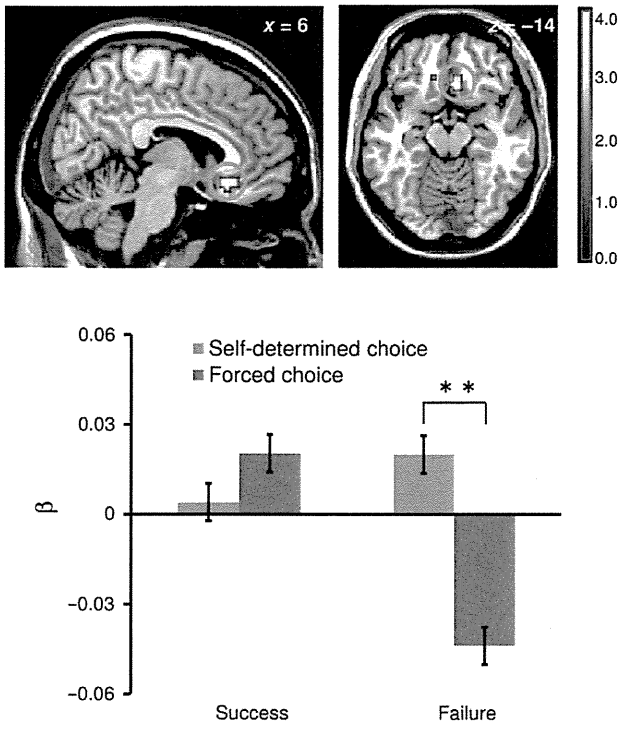


Figure 5. Right vmPFC activation (peak at 6, 26, −14) showing a significant choice condition by outcome feedback interaction in response to task feedback ($P < 0.05$, familywise error corrected; the image is shown at $P < 0.001$, uncorrected). Neural responses are displayed in sagittal and transaxial formats. The bottom panel represents the mean β values (a 6-mm sphere centered on the peak) and corresponding SEs as a function of choice condition (self-determined choice vs. forced choice) and outcome feedback (success vs. failure). The plot indicated that, in response to success feedback, the vmPFC activation in the self-determined-choice condition was not different from that in the forced-choice condition ($F_{1,50} = 0.70$, $P = 0.41$). On the other hand, the self-determined-choice condition showed higher vmPFC activation when compared with the forced-choice condition in response to failure feedback ($F_{1,50} = 14.11$, $P < 0.01$).

$P < 0.01$). That is, whereas vmPFC activation in the forced-choice condition decreases in response to failure when compared with success feedback ($F_{1,50} = 6.58$, $P = 0.01$), which is consistent with the previous literature (Hare et al. 2008; Noonan et al. 2011), this pattern was not observed in the self-determined-choice condition ($F_{1,50} = 0.58$, $P = 0.45$). In other words, the self-determined choice, relative to forced choice, buffered the decreased activation in the vmPFC in response to the negative feedback.

In our experiment, the forced-choice condition had a larger number of trials and produced more failure trials (see Behavioral results). Therefore, the decrease in the vmPFC in response to failure in the forced-choice condition might merely reflect the habituation to failure that was specific to the forced-choice condition. To address this possibility, we ran another GLM that included the cumulative number of failure experiences for each condition as a trial-specific parametric modulator. This parametric modulator was separately modeled for self-determined-choice and forced-choice conditions in response to failure feedback. The number of failure experiences was not significantly related to the vmPFC deactivation in either condition ($P < 0.05$, familywise error corrected), even with a more lenient criterion ($P < 0.005$, uncorrected). We also conducted a $2 \times 2 \times 3$ ANOVA with choice condition (self-determined choice or forced choice), outcome feedback (success or failure), and session (sessions 1–3) as factors within each ROI, in order to investigate whether our findings were moderated by practice effect (see our behavioral analysis). None of our main findings in the striatum and the vmPFC significantly interacted with the session.

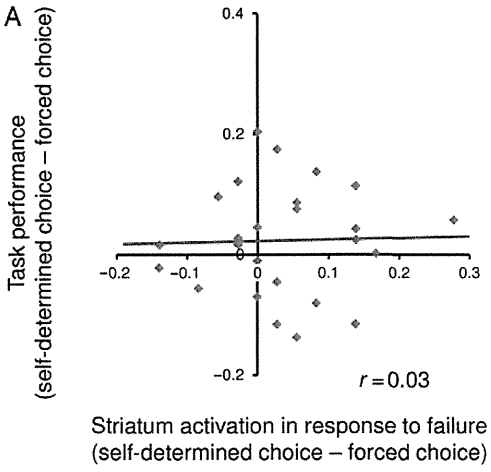
Finally, to confirm that the activation pattern in the striatum and vmPFC were statistically different, we further conducted a $2 \times 2 \times 2$ ANOVA with choice condition, outcome feedback, and brain region (striatum vs. vmPFC) as factors. The analysis showed a three-way interaction ($F_{1,25} = 4.09$, $P = 0.05$), indicating that the striatum and vmPFC functioned differently in self-determined-choice and forced-choice conditions in response to outcome feedback.

The vmPFC result is in marked contrast with the striatum findings, and suggests the possibility that the enhanced task performance in the self-determined-choice condition may be related to this modulation effect in the vmPFC activation in response to failure feedback. To examine whether the differential vmPFC activation in response to failure feedback was indeed related to the enhanced task performance, we further conducted a brain–behavior correlation analysis. Specifically, we indexed the magnitude of brain resilience in the self-determined-choice condition by subtracting the β value in the forced-choice condition from the β value in the self-determined-choice condition in response to failure feedback. We also indexed the performance advantage in the self-determined-choice condition by subtracting the task performance in the forced-choice condition from that in the self-determined-choice condition. The performance advantage was uncorrelated with overall task performance ($r = 0.06$, $P = 0.75$), indicating that this index does not merely reflect overall task performance or general motivation for the task. Our analysis revealed a significant positive correlation between these 2 indices ($r = 0.40$, $P < 0.05$), indicating that those who showed less drop in the failure-induced brain activity in the self-determined-choice condition (when compared with the forced-choice condition) exhibited a larger performance enhancement effect caused by self-determined choice (Fig. 6*B*).

We then conducted the same correlational analysis for the striatum activation, but the correlation was not significant ($r = 0.03$, $P = 0.89$; see Fig. 6*A*). This finding provides further evidence for the functional dissociation between the striatum and the vmPFC. We also performed the same correlational analysis focusing on the brain activation in responses to success feedback. Neither the vmPFC nor striatum showed significant correlation ($r = -0.21$ and 0.10, P's > 0.31), suggesting that the observed correlation is specific to failure feedback.

Brain Activation in Response to Task Initiation

For exploratory purpose, we also examined the brain activation associated with self-determined choice during task initiation (when they pressed a button to start the stopwatch; see Fig. 1*A*). A whole-brain analysis showed that task initiation in the self-determined-choice condition (in comparison to the forced-choice condition) increased brain activation in the pre-SMA(extending into the superior frontal gyrus; $P < 0.001$ uncorrected), which is implicated in the initiation of self-generated (or voluntary) action (Fig. 7; Haggard 2008; Passingham et al. 2010). This comparison also revealed other areas of significant activation, including superior frontal gyrus, midbrain, and cerebellum ($P < 0.001$ uncorrected; see Table 3). No



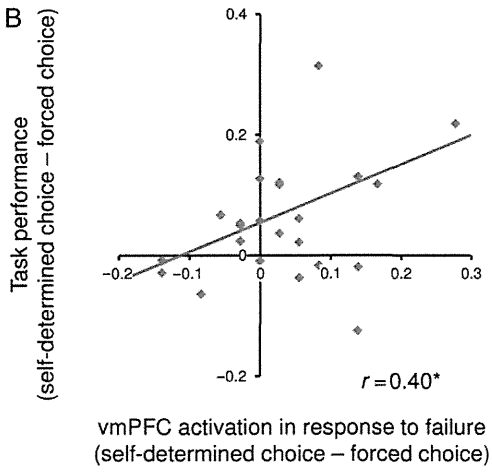


Figure 6. (*A*) Correlation between the promoted task performance due to self-determined choice (*y*-axis) and the magnitude of the striatum resilience in the self-determined-choice condition (computed by subtracting the β values in the forced-choice condition from the β value in the self-determined-choice condition in response to failure feedback; *x*-axis). No significant positive correlation was observed ($r = 0.03$, $P = 0.89$), indicating that the striatum may be unrelated to promoted performance and motivation due to self-determined choice. (*B*) Correlation between the promoted task performance due to self-determined choice (*y*-axis) and the magnitude of the vmPFC resilience in the self-determined-choice condition (computed by subtracting the β values in the forced-choice condition from the β value in the self-determined-choice condition in response to failure feedback; *x*-axis). Significant positive correlation was observed ($r = 0.40$, $P < 0.05$), indicating that those who showed less activation drop in the self-determined-choice condition in response to failure feedback tended to show enhanced task performance in the self-determined-choice condition.

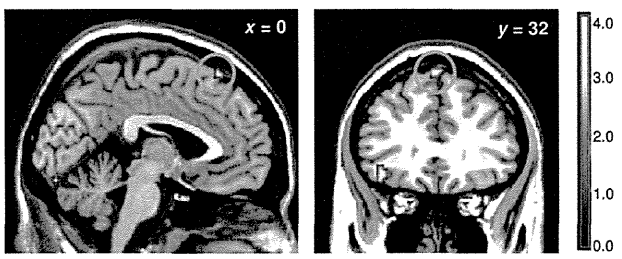


Figure 7. Pre-SMA responses elicited by self-determined-choice trials relative to forced-choice trials when participants initiated the task (i.e., when participants pressed a button; $P < 0.001$, uncorrected). Neural responses are displayed in coronal and transaxial formats.

Table 3
Effects of self-determined choice during task initiation period

Region	Peak MNI coordinates			*t* value	*k*
	x	*y*	*z*		
Self-determined choice > forced choice					
R/L. Presupplementary motor area	0	35	61	3.48	8
R. Middle temporal gyrus	66	−19	−17	4.98	30
R. Central orbitofrontal cortex	36	41	−11	3.84	10
L. Central orbitofrontal cortex	−39	32	−14	3.68	12
L. Middle temporal gyrus	−60	−10	−26	3.47	6
Forced choice > self-determined choice	(No significant activation)				

Results of a whole-brain analysis showing higher activation in the self-determined-choice condition than in the forced-choice condition during the task initiation period (i.e., when participants started a stopwatch task; $P < 0.001$, uncorrected, $k \geq 5$ voxels). No areas showed significantly higher activation in the forced-choice condition than in the self-determined-choice condition. *k*, number of significant voxels.

brain region showed stronger activation in the forced-choice condition than in the self-determined-choice condition. Additional GLM model including task initiation time as a parametric modulator did not show any significant brain activations associated with the task initiation time ($P < 0.001$ uncorrelated).

Functional Connectivity Analysis Between Cue and Feedback Periods

Finally, to explore possible mechanisms underlying the buffering effect of the self-determined choice in response to failure feedback, we conducted a functional connectivity analysis between the brain activation during the cue period and the vmPFC activation during the feedback period. We were especially interested in the connectivity in the self-determined-choice condition in response to failure feedback. Accordingly, we examined the brain areas whose activation during the cue period showed stronger functional connectivity with the vmPFC activation in response to feedback in the self-determined-choice/failure condition than in the other 3 conditions (i.e., self-determined-choice/success, forced-choice/success, and forced-choice/failure). We used the peak voxel from the vmPFC region that exhibited a significant interaction (Fig. 5) as the seed of the connectivity analysis. Given the exploratory nature of the analysis and relatively low statistical power to detect difference in functional connectivity across conditions, we used a relatively lenient threshold ($P < 0.01$, uncorrected, $k \geq 10$). Only 3 brain areas survived the statistical test, including the central orbitofrontal cortex, a brain area closely related to the vmPFC (Table 4). These results indicate that, when participants received negative feedback in the self-determined-choice condition, the within-person fluctuation of the OFC activation during the cue period is more positively correlated with that of the vmPFC activation during the outcome feedback period, than when participants received feedback in the forced-choice condition or when participants received positive feedback in the self-determined-choice condition.

Discussion

The current study provides the evidence that activation in the vmPFC in response to failure feedback for an achievement task is modulated by self-determined choice. More specifically, our neuroimaging results showed that self-determined choice (when compared with forced choice) prevented the drop in

Table 4

Brain areas that showed stronger functional connectivity with the vmPFC activation in response to negative feedback in the self-determined-choice condition (cue period)

Region	Peak MNI coordinates			*t* value	*k*
	x	*y*	*z*		
Self-determined choice > forced choice					
R. Central orbitofrontal cortex	21	29	−17	3.18	19
R. Superior frontal gyrus	24	14	67	3.12	39
L. anterior cingulate cortex	−6	20	−11	2.75	10

This functional connectivity analysis examined the brain activation during the cue period which has trial-by-trial connectivity with the vmPFC activation during the outcome feedback period. Results show a whole-brain analysis indicating stronger functional connectivity in the self-determined-choice condition with negative feedback than in the self-determined-choice condition with positive feedback and in the forced-choice condition with positive and negative feedback ($P < 0.01$, $k \geq 10$ voxels). *k*, number of significant voxels.

the vmPFC activation (i.e., negative reward value) in the face of failure feedback, and this was related to the enhanced task performance in the self-determined-choice condition. It is worth noting that participants knew that choice options were different only in their physical appearance, which is clearly irrelevant to task difficulty. Despite this subtle manipulation, we found that self-determined choice promoted task performance and modulated the vmPFC activation.

A critical question that arises is why the vmPFC activation did not drop in response to negative feedback in the self-determined-choice condition. When people ongoingly work on an achievement task, some failure is essentially unavoidable. Most literature in decision neuroscience assumes that such failures have immediate negative reward value, and in fact, failure has been regarded as the source of many psychiatric symptoms (e.g., depression; Seligman 1975). Studies which observed the drop in the vmPFC activation in response to negative feedback (relative to positive feedback) interpreted their findings based on this scheme (e.g., Daniel and Pollmann 2010). Yet negative feedback can serve to provide important information that may minimize further errors and improve people's performance in the long run (Carver and Scheier 1998). In other words, people can treat the negative feedback as useful information for improving their own future performance—this is referred to as interpreting feedback informationally (Ryan 1982; Deci and Ryan 1985). As such, to maintain optimal performance, it would appear that it is critical for people to offset the negative emotional value of failure by treating the feedback informationally and thus embracing the positive experience of using the feedback on their own behalf.

We speculate that this informational processing of negative feedback to be a critical mechanism underlying the facilitative effect of self-determined choice on performance. In fact, several behavioral studies have shown that self-determined choice reduces individuals' vulnerability to failure experiences (Mikulincer 1988; Moller et al. 2006; see also Legault and Inzlicht 2013). Thus, the absence of the drop in the vmPFC activation in response to failure may reflect the possibility that self-determined choice oriented people toward experiencing the negative feedback informationally, interpreting it in terms of its value for enhancing future performance and attaining future positive outcomes. In accord with this interpretation, there is substantial body of research indicating the role of the vmPFC in updating outcome value (Rolls 2004) or future outcome expectations (Schoenbaum et al. 2009). Our functional connectivity analysis also implied that trial-by-trial fluctuation of choice value (as reflected in the OFC activation) predicted the extent to which participants were resilient to failure feedback in the self-determined-choice condition (as indicated by the smaller vmPFC decrease) more than it did in the other conditions.

It is important to note that our data showed the modulation effect of self-determined choice only in the vmPFC, and not in the striatum. The vmPFC and striatum are directly connected brain structures that have been strongly implicated in reward-related processing (Haber and Knutson 2010), but their functional dissociation has not been well documented in the literature, except for a relatively few cases (Hare et al. 2008; Knutson et al. 2001). We speculate that, in contrast to the vmPFC, the striatum may entail crude and automatic valuation processes that are relatively insensitive to the context. It has been well established in the psychological literature that the human evaluation process is supported by 2 qualitatively different systems—an automatic, general process and an elaborative, context-specific process (dual process model; Cacioppo and Petty 1985; Kahneman 2003; this dichotomy may possibly be related to the distinction between model-free and model-based mechanisms in reinforcement learning, which attracts recent attention in decision neuroscience; Daw et al. 2011; O'Doherty 2012). It is possible that this distinction may map onto the functional dissociation between the striatum and vmPFC observed in the present experiment. In fact, previous research indicated that initial crude evaluation is made in the ventral striatum/pallidum, whereas the vmPFC is involved in the re-organization of already formed evaluations initially mediated by the striatum (Kim et al. 2007; but see also Lieberman 2007). Another line of research also suggests a relation between the vmPFC and impulse control (Bechara et al. 2000). This idea is also consistent with the fact that the vmPFC has strong anatomical connection with the medial prefrontal cortex and ACC, both of which have been implicated in top-down modulation in the cognitive and affective value computation (Matsumoto et al. 2003; Botvinick et al. 2004). Although researchers have agreed that vmPFC activation is correlated with reward value, the precise nature of value representation in the vmPFC is still debated (Rushworth et al. 2011). At least, accumulating evidence suggests that the vmPFC represents more than a passive assessment of objective value (e.g., Boorman et al. 2009). Our findings may have potential to contribute to this ongoing discussion.

The insensitivity of the striatum to the outcome of self-determined choice, however, should be interpreted with caution. On the one hand, this insensitivity nicely corroborates with a recent study (Kool et al., 2013) examining the neural correlates of the classic phenomenon "illusion of control" (Langer 1975). In this study, participants showed higher estimates of reward probability for gambles they had chosen than for identical gambles that were imposed. Despite the increase in subjective reward probability, however, the striatal activation in response to outcome was unaffected by whether participants made a choice or not. On the other hand, there is a line of research showing that the striatal activation to outcome feedback is modulated by the perceived connection between action and outcome (Tricomi et al. 2004, 2006). For example, Tricomi et al. (2004) showed that, using a probabilistic task, the striatal activation decreased in response to punishment more in choice condition (i.e., participants could choose an option which they believe to lead to reward) than in no-choice

condition. Further studies are needed to examine the effects of self-determined choice on the striatal activation in response to outcome feedback.

Our experiment also replicated a previous study showing that anticipation of choice recruits activity in the dorsal ACC, insula, ventral pallidum, and midbrain (Leotti and Delgado 2011). Both the dorsal ACC and anterior insula have been implicated in a variety of cognitive and motivational functioning, such as cognitive control, conflict monitoring, and emotional awareness (Botvinick et al. 2004; Craig 2009). This suggests that self-determined choice requires emotional and cognitive commitment to the task. This conjecture is also consistent with a recent fMRI study showing that the anterior insula is related to self-determined reasons for behavior (Lee and Reeve 2013). The ventral pallidum and midbrain have been related to reward processing (Pessiglione et al. 2007; Mobbs et al. 2009), and as such, our findings suggest that there is inherent reward value in self-determined choice (Leotti and Delgado 2011). It should be noted, however, that our experiment has fewer self-determined-choice trials than forced-choice trials to control for item selection bias, and it is possible that the observed activation in response to the self-determined choice trials represents cue saliency (Litt et al. 2011). Although our findings were consistent with the previous study that controlled for cue saliency (Leotti and Delgado 2011), this issue should be addressed in future research. As another side note, we observed somewhat weaker activation in the ventral pallidum. This may reflect the fact that our experimental task has smaller incentive value than the task used in the previous study. Indeed, unlike the previous study, participants were not provided with any monetary rewards and were explicitly instructed that choice of stopwatch is irrelevant with task difficulty. Thus, self-determined choice did not convey any information about the immediate reward value in our experimental task.

An interesting finding for our exploratory analysis in the task initiation period (i.e., when participants press a button to start the task) is the pre-SMA activation in the self-determined-choice condition. Previous studies have indicated that the pre-SMA is involved in the initiation of self-generated action—action that people choose to perform without any external cues (Rushworth et al. 2004; Haggard 2008; Passingham et al. 2010). At a glance, this may lead people to think that the pre-SMA activation reflects self-generated action, as self-generated action seems to bear close resemblance to self-determined choice. Yet, the interpretation may not be as straightforward as it seems, because the task initiation was actually voluntary regardless of the choice conditions in our experiment—participants could freely determine the time to start the stopwatch in both the self-determined choice and forced-choice conditions. Perhaps our results indicate that not all the self-generated actions are equal: Even when people can determine the timing to initiate the same task, the subjective sense of freedom to initiate the task may be different depending on contextual factors such as task instructions. Future work would do well to examine factors that elicit subjective sense of self-determination in self-generated action.

The present study provided evidence that self-determined choice has beneficial effects on performance. Yet it is not entirely clear why self-determined choice has such an effect, even when people know that their choice is irrelevant to the ultimate outcome. This may reflect an evolutionarily innate human need for autonomy (Deci and Ryan 1985) or prior learning experiences in which self-determined choice led to positive outcomes (learned belief in personal control; Huys and Dayan 2009). Work on separating these effects, although conceivably difficult, would greatly contribute to theoretical advancement in the fields of motivation and neuroscience.

Funding

This study was supported by a Grant-in-Aid for Scientific Research (A#24240061; to K.Matsumoto), a Grand-in-Aid for Scientific Research on Innovative Areas "The study on the neural dynamics for understanding communication in terms of complex hetero systems (No. 4103)" (#24120717; to K.Matsumoto), and Tamagawa University Global Center of Excellence grant from the Ministry of Education, Culture, Sports, Science, and Technology, and a Grant from the Ministry of Health, Labour, and Welfare (H24-seishin-ippan-002; to K.Matsumoto) Japan.

Notes

The authors thank M. Walton, M. H. Immordino-Yang, M. Botvinick, and J. Reeve for helpful comments; T. Haji, and J. Gläscher for technical advice; the Alexander von Humboldt Foundation for fellowship support (to K.Murayama). *Conflict of Interest*: None declared.

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