Incentive Sensitivity as a Behavioral Marker of Clinical Remission From Major Depressive Episode

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ABSTRACT

Background: Reduction of goal-directed behaviors is frequently observed in depression and may be linked to dysfunction of incentive motivation process.

Objective: To investigate whether incentive sensitivity could constitute a behavioral marker of clinical remission in major depression.

Methods: A handgrip force measurement device was employed to assess the impact of incentive motivation and emotional manipulation on the effort produced by remitted patients (n = 20) compared to matched depressed patients (n = 22) and healthy controls (n = 26). Depressed and remitted patients fulfilled the major depressive disorder *DSM-IV* criteria for current episode and remission state, respectively. The study was performed between March and July 2013.

Results: Relative to patients with acute depression, patients after remission retrieved a normal sensitivity to incentives ($t_{1,40} = 4.18$, $P < 1.5 \times 10^{-4}$), but relative to healthy controls, they kept an abnormally high susceptibility to emotional arousal ($t_{1,44} = 2.4$, $P = .02$). Normalization of incentive sensitivity exhibited in the behavioral test was associated with improvement of apathy measured on the clinical scale.

Conclusions: Using a simple behavioral paradigm at patients' bedside, we could identify the factors influencing effort production, so as to discriminate remitted patients from both depressed patients and healthy controls.

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The current criteria for major depressive disorder (MDD) define a highly heterogeneous clinical syndrome, and patients fulfilling the diagnostic criteria of MDD do not necessarily share any symptom at all. Thus, redefinition is necessary and may require focusing on a more narrow set of core symptoms, as recently claimed by the National Institute of Mental Health (NIMH) in the Research Domain Criteria project.[1] Emotional dysregulation[2] and approach motivation[3,4] might be the core clinical dimensions involved in MDD. In this study, we explore the impact of these 2 dimensions on behavior intensity during a major depressive episode and after recovery.

Motivation can be construed as the amount of energy that an individual is willing to invest in order to attain a goal.[5] To measure energy, our team has developed a paradigm in which participants squeeze a power grip related to a dynamometer. The goal is to win as much money as possible, knowing that payoff is proportional to the amount of force exerted on the grip. The goal value is manipulated by varying the amount of money at stake (ie, incentive level) on a trial-by-trial basis. In previous functional magnetic resonance imaging studies,[6–8] we found that incentive level was reflected in the ventral striatopallidal complex, a region that is dysfunctional in MDD.[9] Consistently, the force exerted by depressed patients was not modulated by monetary incentives, contrary to what was observed in healthy volunteers.[10] Moreover, even if patients objectively failed to exert more effort for higher incentives, they subjectively felt as if they were trying harder (as measured by effort rating). We therefore suggested that incentive motivation impairment is a core deficit of MDD, which may render everyday tasks abnormally effortful for patients.

Emotional state has also been manipulated within the same paradigm by showing pictures from the International Affective Picture System prior to effort exertion.[11] This emotional manipulation has been previously shown to enhance force production via another brain system, including the anterior insula.[12] The emotional arousal induced by these pictures, irrespective of their valence (positive or negative), helped depressed patients exert more effort.[10] In contrast, matched control subjects managed to filter out these emotional distractors and based their effort solely on monetary incentives. A critical question is whether the inverse pattern observed in depressed patients—behavior intensity being sensitive to emotional arousal but not incentive motivation—is a trait marker of depression or is dependent upon the clinical status. If a trait marker, it would offer some insight into the vulnerability that may lead to depression. If a state marker, it would offer a tool for assessing the progression to, and recovery from, depressive episodes. To move forward on this issue, we employed in the present study the same behavioral paradigm so as to assess the evolution of the emotional and motivational effects from major depressive episode to clinical remission.

Clinical Points

- Loss of motivation is a frequent complaint in major depressive disorder that remains difficult to assess. This study investigated the use of a behavioral test that measures incentive motivation—the willingness to make more effort to earn more reward.
- Incentive motivation followed the evolution of clinical status: it was impaired during depressive episode and normalized after remission linked to antidepressant treatment.

METHODS

Participants

The study was approved by the Pitié-Salpêtrière Hospital ethics committee and was supported by the INSERM (the French National Institute of Health). All patients gave written informed consent prior to participation, and all data were recorded anonymously. The study was performed between March and July 2013.

A total of 20 remitted outpatients were recruited from the Pitié-Salpêtrière Hospital (Paris, France) and Château de Garches Clinic (Garches, France). All patients fulfilled the *DSM-IV* criteria for a recurrent MDD (excluding bipolar disorders) and were in remission for at least 6 months (mean = 27.9 months; minimum, 6; maximum, 120). Diagnoses were made using the Mini-International Neuropsychiatric Interview (MINI)[13] and classical psychiatric examination. Remission was defined by a Montgomery-Asberg Depression Rating Scale (MADRS)[14] score lower than 10 and a Hospital Anxiety and Depression Scale-depressive (HAD-D)[15] score lower than 7. Exclusion criteria were age under 18 years, depression with psychotic features, psychiatric comorbidity (notably severe personality and anxiety disorders such as obsessive-compulsive disorder or social anxiety disorder), neurologic illness, other medical conditions susceptible to affect cognition, current and/or past diagnosis of substance (drug and alcohol) abuse, and administration of electroconvulsive therapy in the preceding 12 months. Most patients (15 of 20) were receiving maintenance medication (Supplementary eTable 1), mostly selective serotonin reuptake inhibitors or serotonin-norepipephrine reuptake inhibitors.

The group of remitted patients was compared to depressed patients (n = 22) and healthy controls (n = 26) recruited for a previous study[10] from the same clinics and was also assessed with the MINI (Table 1 depicts comparison). There was no significant difference between controls, depressed patients, and remitted patients in terms of age or gender and no significant difference between patients on every relevant clinical feature (including the number of past depressive episodes).

Table 1. Demographic and Clinical Features[a]

Feature	Remitted Group	Depressed Group
Gender, n		
Female	13	17
Male	7	5
Age, y	42.6 ± 10.8	43.3 ± 2.9
MADRS score	4.0 ± 2.9	31.8 ± 1.0
HAD-A score	5.4 ± 2.4	14.0 ± 0.9
HAD-D score	3.1 ± 3.2	13.4 ± 0.8
Starkstein Apathy Scale score	9.4 ± 4.1	20.9 ± 1.3
No. of depressive episodes	2.3 ± 1.3	2.7 ± 0.5
FAST scale (functioning)	14.9 ± 10.5	NA

[a]Data are mean ± intersubjects standard errors, except where otherwise noted.
Abbreviations: FAST = Functional Assessment Staging Scale, HAD-A = Hospital Anxiety and Depression Scale-anxiety, HAD-D = HAD-depressive, MADRS = Montgomery-Asberg Depression Rating Scale, NA = not assessed.

Data Acquisition

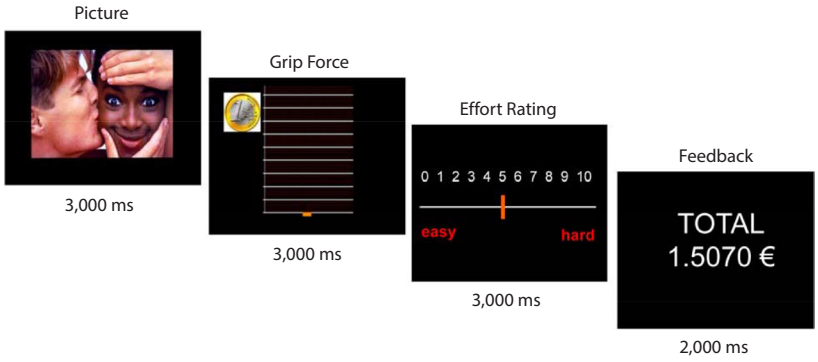
The behavioral tests were conducted just after completion of the clinical scales reported in Table 1. The task has been previously described in detail.[10] The maximal force was measured before starting the experiment and served to calibrate the scale that served to give subjects visual feedback on the force produced. After receiving instructions, subjects were trained on a short practice version (9 trials) in order to become familiar with stimulus presentation and handgrip manipulation. The subjects were instructed to squeeze the handgrip to win as much money as possible. The task was made up of 12 repetitions of 9 trial types, for a total of 108 trials, grouped in a single session lasting about 20 minutes. The trial types were generated according to 3 emotional categories (negative, neutral, and positive) and to 3 monetary incentives (1c, 10c, and €1). Emotional categories and monetary incentives were randomly distributed over the trials, and the sequence was fixed such that patients and controls were assessed on the exact same task.

In every trial (Figure 1), subjects first watched a new emotional picture displayed on screen for 3,000 milliseconds. They were told that the content of these pictures would not influence the amount of money they could win. A graduated scale then appeared on screen together with a coin image indicating the amount of money at stake. This was the cue for subjects to squeeze the handgrip so as to move the cursor up as high as possible, within a 3,000-millisecond interval. Subjects were aware that the height they reached within the scale determined the fraction of the monetary stake they would keep. On the subsequent screen, subjects were asked to rate the effort exerted when squeezing the handgrip. They were asked, "How hard did you try?" and were encouraged to report their feeling and to not rely on visual feedback (cursor height). To indicate their rating, subjects had to move a cursor within a scale graduated from 0 ("easy": minimal effort) to 10 ("hard": maximal effort). They used the keyboard to move the cursor right and left and had 3,000 milliseconds to reach the appropriate position. At the end of each trial, feedback on the cumulative money won so far was presented for 2,000 milliseconds.

Data Analysis

Two dependent variables were considered: objective grip force and subjective ratings of perceived effort. In our

Figure 1. Behavioral Task[a]



[a]Successive screenshots displayed in 1 trial are shown from left to right, with durations in milliseconds. Neutral or arousing pictures (with positive or negative valence) were shown prior to physical effort exertion. Effort was cued by simultaneously showing the amount of money at stake, materialized as coin images (1c, 10c, or €1), and a graduated scale in which a cursor represented the force exerted on the handgrip. Subjects knew that the top of the scale corresponded to the monetary incentive, such that the more they squeezed the handgrip, the more money they would win. After force production, subjects rated the extent of their effort by positioning a cursor on an analog scale. The final screen informed subjects about the cumulative total of monetary earnings.

experimental design, the controlled factors were incentive levels and emotional picture categories. To analyze grip force, we extracted in every trial the area under the curve over the 0- to 6-second period following onset of the coin image. Grip force was expressed as a percentage of the highest measure recorded during task completion in order to eliminate individual differences in maximal power. Effort ratings were divided by the actual force produced, on a trial-by-trial basis, in order to get an index of subjective effort sensation for a same objective force of 1 N. The *incentive effect* was defined as the difference between €1 and 1c. As in our previous study,[11] we defined an *arousal effect* as the difference between emotional (averaging positive and negative) and neutral pictures, since we found no difference between negative and positive pictures on force production.

Although they included 1 newly collected and 2 previously acquired datasets, the following analyses are entirely novel. They aim at comparing incentive and arousal effects between the new group (remitted patients) and the 2 others (depressed and controls). General linear models (GLMs) were built in order to explain the trial-by-trial variability in both objective and subjective force production. The 2 factors of interest were included as parametric regressors modeling incentive levels (1c, 10c, or 1€) and arousal levels (1, 0, and 1 for positive, neutral, and negative pictures, respectively). The GLM also included a constant term, which reflects the individual susceptibility to perform the task (how much one squeezes the grip outside incentive or arousal effects) and trial number, which indexes fatigue accumulation throughout the task. All regressors were standardized (*z*-scored) before GLM estimation. Regression coefficients (β values) were estimated at the individual level and then tested for statistical significance at the group level (using 1-sample, 1-tailed *t* test). When appropriate, post hoc comparisons between groups were performed on β estimates using 2-sample, 2-tailed *t* tests.

We then examined whether incentive or arousal effects could accurately classify individuals into the different control and patient groups, using receiver operating characteristic (ROC) curves. We also tested correlations of incentive and arousal effects on force production with various clinical scores. Depressed and remitted groups were pooled in order to have a greater variance to explain. Two separate GLMs were conducted for incentive and arousal effects with Starkstein Apathy Scale,[16] MADRS, HAD-D, and HAD-anxiety (HAD-A) scores as regressors. These regressors were orthogonalized relative to putative confounding factors, namely, group, age, gender, and number of past depressive episodes. These confounding factors were also included in the GLM to ensure that they could not drive the correlations. This was particularly important for the group factor since the difference between remitted and depressed patients could have artificially created correlations between clinical variables and experimental measures. By design, depressed patients were tested before treatments could have an effect (at a mean ± standard error of the mean [SEM] of 5.4 ± 0.4 days after treatment onset), so we could not include treatment as an additional regressor in the main GLM estimated across groups.

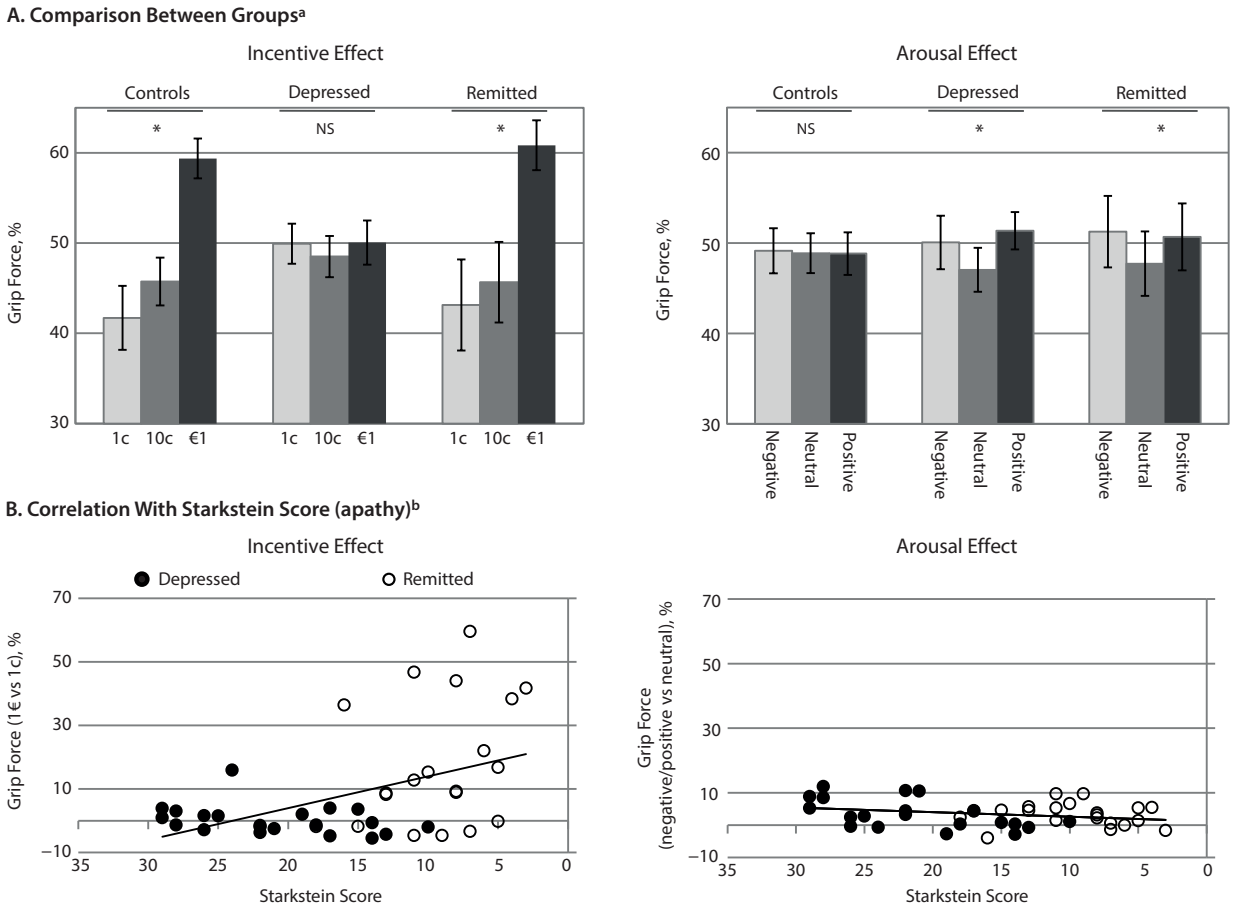
All statistical tests were conducted with the MATLAB statistical toolbox (MATLAB R2013a, MathWorks, Inc).

RESULTS

We first examined measures of maximal force and found no difference between remitted patients and the 2 other groups. The absolute maximal force (mean ± SEM) in remitted patients (290 ± 17 N) was intermediate between healthy controls (313 ± 20 N, $t_{44} = 0.8$, $P = .3$) and depressed patients (255 ± 22 N, $t_{40} = 1.2$, $P = .2$).

We then analyzed the data acquired during the task, starting with the main dependent measure, objective

Figure 2. Dissociation of Incentive and Arousal Effects on Force Production



[a]Histograms show the effects of the main independent factors, incentive level (from 1c to 1€), and arousal level (emotional vs neutral ones) on the main dependent variable (grip force). Grip force is expressed as a percentage of the highest measure. Error bars are intersubjects standard errors of the mean.
[b]Incentive (left) and arousal (right) effects are plotted against individual scores obtained on Starkstein Apathy Scale. Filled and empty circles are depressed and remitted patients, respectively. The x-axis has been reversed to illustrate clinical improvement from left to right. Regression lines represent the best linear fit.
*Significant difference from 0 (*t* test, $P < .05$) obtained for incentive and arousal regression coefficients from general linear models.
Abbreviation: NS = nonsignificant.

handgrip force, which was regressed against incentive level, arousal level, trial number, and a constant term separately for each of the 3 groups. In our control sample, force production was significantly explained by incentive level ($t_{1,25} = 5.1$, $P < 10^{-4}$), trial number ($t_{1,25} = -2.5$, $P = .01$), and the constant term ($t_{1,25} = 21$, $P < 10^{-4}$), but not by arousal level. There was no interaction between factors.

In our depressed group, force production was significantly explained by arousal level ($t_{1,21} = 3.3$, $P = .02$), trial number ($t_{1,21} = -4.8$, $P < 10^{-4}$), and the constant term ($t_{1,21} = 21$, $P < 10^{-4}$), but not by incentive level. There was no interaction between factors.

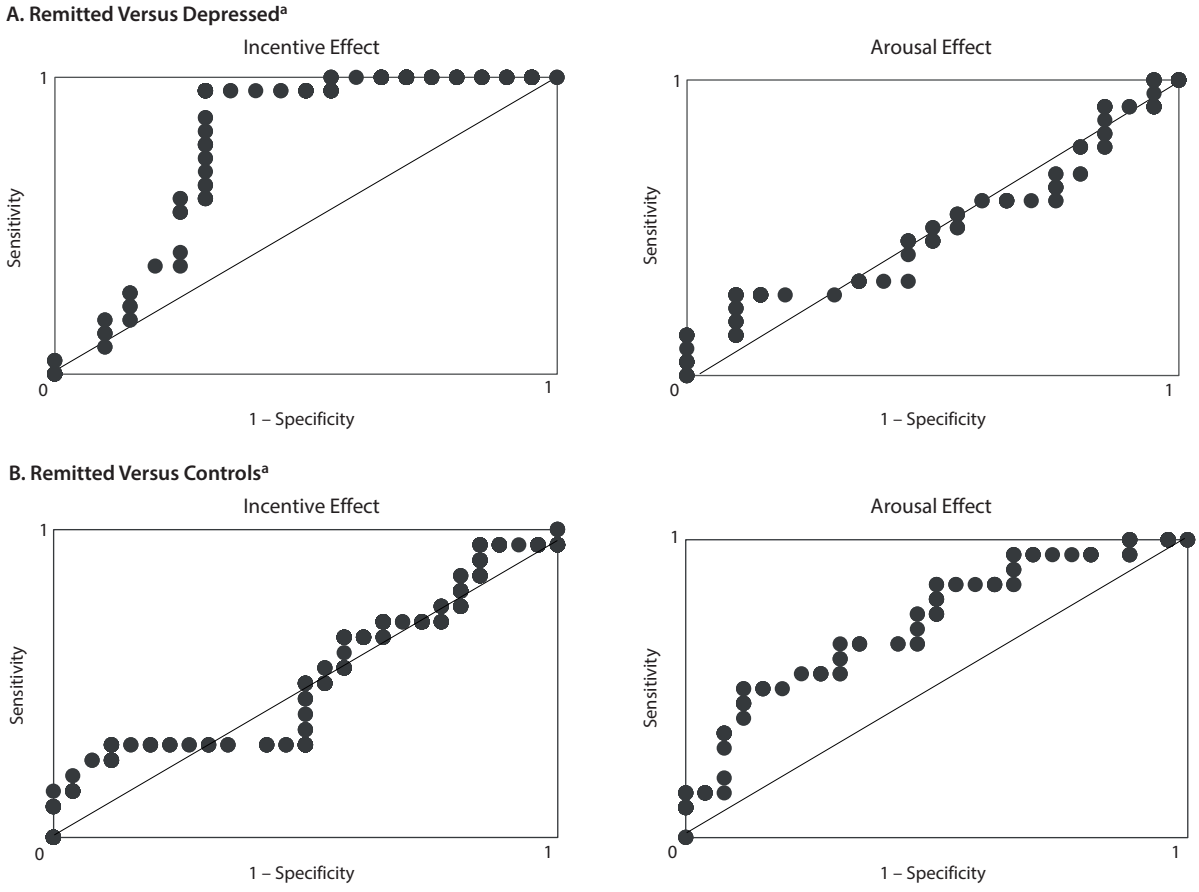
When comparing remitted patients to depressed and healthy control groups (Figure 2A), we found a significant difference with healthy controls only in the arousal effect ($t_{1,44} = 2.4$, $P = .02$) and, with depressed patients, only in the incentive effect ($t_{1,40} = 4.18$, $P < 1.5 \times 10^{-4}$). Thus, remitted patients had recovered a normal sensitivity to incentive manipulation but kept an abnormal sensitivity to emotional inducement.

The same analyses were conducted for subjective effort. In our previous study,[10] subjective effort was influenced by incentive level and emotional arousal: effort was less painful when more money was at stake and when pictures were more arousing. These effects were not significant in remitted patients. However, since there was no significant difference with controls, the analysis of subjective effort remains inconclusive.

Then we looked for clinical variables (Starkstein Apathy Scale, MADRS, HAD-A, or HAD-D scores) that could account for the differences observed between depressed and remitted groups in the incentive and arousal effects on objective grip force. The incentive effect was significantly predicted by age ($t_{1,32} = -1.8$, $P = .03$) and Starkstein Apathy Scale score ($t_{1,32} = -1.75$, $P = .04$). In contrast, arousal effect was not correlated with any clinical variable (for apathy score, see Figure 2B).

Because the pattern of force modulation by incentive and arousal levels was clearly different between the 3 groups, we investigated whether it could be used as a behavioral marker

Figure 3. Discrimination of Groups Using Receiver Operating Characteristic Curves



[a]Each cross shows sensitivity (true-positive rate) and 1 – specificity (false-positive rate) obtained with a given criterion set on incentive or arousal effect on force production. Note that remitted patients were better distinguished from depressed patients using incentive effect (A), and from controls using arousal effect (B).

allowing discrimination of remitted patients from both depressed and controls (Figure 3). The ROC curves showed that the incentive effect was the best marker to distinguish depression status (ongoing episode vs achieved remission), with 95% sensitivity and 70% specificity (Figure 3A). To distinguish between remitted patients and healthy controls, the best marker was arousal effect, with 95% sensitivity and 65% specificity (Figure 3B).

DISCUSSION

This study was designed to explore how the sensitivity of effort production to emotional and motivational factors varies with the progression of clinical status. Previous results[10] suggested that acute depression was characterized by null sensitivity to incentive motivation associated with hypersensitivity to emotional inducement. Present results show that these 2 features evolve differently with clinical remission: incentive motivation effects were totally retrieved, while emotional sensitivity was still abnormally high (irrespective of valence). The other factors influencing force production, trial number (a proxy for fatigability) and the constant term (a proxy for the willingness to perform the effort task), were not different between depressed patients and healthy controls.

In previous studies, we suggested that incentive and arousal effects were independent since they could be dissociated between patients and controls[10] and because they were shown to recruit separate brain circuits.[12] The present results support this idea by demonstrating that only the incentive effect, and not the arousal effect, normalizes with clinical remission. This shows that the motivational deficit observed in depressed patients was not a consequence of a failure to filter out emotional capture, since remitted patients exhibited normal motivational effects in the presence of abnormal emotional effects. It therefore appears that dysfunction of incentive motivation was a state-dependent deficit rather than a trait-related one. By contrast, emotional sensitivity was not state dependent. However, we could not disentangle whether this was related to a personality trait leading to MDD or if it was a scar induced by the major depressive episode. To get better insight on this issue, it would be informative to test asymptomatic first-degree relatives of depressed patients. Furthermore, abnormal emotional sensitivity might not be specific to depression; it might be interesting to examine other clinical conditions such as anxiety disorders.

The only clinical variable correlating with the normalization of incentive sensitivity was the apathy score measured using the Starkstein Apathy Scale. By contrast, no clinical variable was associated to emotional arousal effect. Thus, our behavioral marker of MDD clinical status seemed to capture a form of apathy characterized as the inability of patients to exert more effort in order to earn more reward.

Our findings are consistent with the growing literature linking depression to reduced reward sensitivity.[17,18] This deficit has been characterized in different types of tasks, some involving incentive motivation, such as the monetary delay task[19] or the effort expenditure of reward task,[20] others involving reinforcement learning, such as the probabilistic reward learning task.[21] Interestingly, clinical remission from a major depressive episode was associated with recovered incentive motivation[22] but not reinforcement learning.[23] It might be that incentive motivation tasks are more straightforward and do not require additional cognitive abilities that might remain dysfunctional after remission.

Functional neuroimaging studies have associated reduced reward sensitivity with flattened response to reward in the ventral striatum and orbitofrontal cortex, raising hope to develop neural markers of illness status.[9,24] However, behavioral markers are obviously less expensive and faster to assess. The task employed here, which directly measures the effect of potential rewards on effort exertion, might be a good candidate to follow clinical status, as it demonstrated a very robust difference between depressed and remitted patients ($P = 10^{-4}$ for the group-level comparison, 95% sensitivity for individual classification).

Another key feature of the task is the dissociation of incentive motivation from emotional arousal effect, which remained abnormal after remission. This might relate to a large body of literature showing abnormal emotional processing in major depression. It might be surprising that we see no effect of valence, given that a negative bias has been repeatedly documented in major depression.[2,25,26] This apparent discrepancy is probably linked to the different type of measurement: contrary to categorization, appraisal, or memory tasks, force production is strongly influenced by vegetative arousal, a rather reduced dimension of emotional reaction.

Our study has some limitations. First, the number of patients was rather low; assessing the robustness of the ROC curves would require a replication sample. Second, to follow more closely the evolution of our behavioral markers with clinical status, it would have been better to test the same patients at different times and make within-subject comparisons. Third, the experimenter was not blind to the mood status, which is hard to implement in practice since depression symptoms are easily noticeable. Fourth, most of the patients were medicated, such that some differences that we attribute to clinical status might be related to treatment, even if we found no direct evidence for this. Fifth, the patients included in our remitted group had quite different clinical histories. Yet, it is remarkable that despite this heterogeneity, the group ended with a fully recovered capacity for incentive motivation.

These results might invite one to reconsider the evaluation of remission in MDD.[27] Motivational loss is a frequent complaint that is currently poorly assessed because it might have different causes such as depreciation of potential rewards (anhedonia) or exacerbation of action costs (fatigability). From this point of view, our handgrip force paradigm is a promising tool. By dissociating incentive and arousal effects on force production, we were able to discriminate remitted patients from both healthy controls and depressed patients, with reasonable sensitivity and specificity. More generally, assessing the different mechanisms enabling effort production in MDD might inform therapeutic orientation and lead to more personalized treatment.

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REFERENCES

1. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry*. 2010;167(7):748–751.
2. Foland-Ross LC, Gotlib IH. Cognitive and neural aspects of information processing in major depressive disorder: an integrative perspective. *Front Psychol*. 2012;3:489.
3. Russo SJ, Nestler EJ. The brain reward circuitry in mood disorders. *Nat Rev Neurosci*. 2013;14(9):609–625.
4. Treadway MT, Bossaller NA, Shelton RC, et al. Effort-based decision-making in major depressive disorder: a translational model of motivational anhedonia. *J Abnorm Psychol*. 2012;121(3):553–558.
5. Berridge KC. Motivation concepts in behavioral neuroscience. *Physiol Behav*. 2004;81(2):179–209.
6. Pessiglione M, Schmidt L, Draganski B, et al. How the brain translates money into force: a neuroimaging study of subliminal motivation. *Science*. 2007;316(5826):904–906.
7. Schmidt L, d'Arc BF, Lafargue G, et al. Disconnecting force from money: effects of basal ganglia damage on incentive motivation. *Brain*. 2008;131(pt 5):1303–1310.
8. Schmidt L, Lebreton M, Cléry-Melin M-L, et al. Neural mechanisms underlying motivation of mental versus physical effort. *PLoS Biol*. 2012;10(2):e1001266.
9. Der-Avakian A, Markou A. The neurobiology of anhedonia and other reward-related deficits. *Trends Neurosci*. 2012;35(1):68–77.
10. Cléry-Melin M-L, Schmidt L, Lafargue G, et al. Why don't you try harder? an investigation of effort production in major depression. *PLoS ONE*. 2011;6(8):e23178.
11. Mikels JA, Fredrickson BL, Larkin GR, et al. Emotional category data on images from the International Affective Picture System. *Behav Res Methods*. 2005;37(4):626–630.
12. Schmidt L, Cléry-Melin ML, Lafargue G, et al. Get aroused and be stronger: emotional facilitation of physical effort in the human brain. *J Neurosci*. 2009;29(30):9450–9457.
13. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for *DSM-IV* and *ICD-10*. *J Clin Psychiatry*. 1998;59(suppl 20):22–33.
14. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
15. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361–370.
16. Starkstein SE, Mayberg HS, Preziosi TJ, et al. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci*. 1992;4(2):134–139.
17. Simmons WK, Drevets WCA. A "taste" of what is to come: reward sensitivity as a potential endophenotype for major depressive disorder. *Biol Psychiatry*. 2012;72(7):526–527.
18. Whitton AE, Treadway MT, Pizzagalli DA. Reward processing dysfunction in major depression, bipolar disorder and schizophrenia. *Curr Opin Psychiatry*.

2015;28(1):7–12.
19. Pizzagalli DA, Holmes AJ, Dillon DG, et al. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *Am J Psychiatry*. 2009;166(6):702–710.
20. Treadway MT, Zald DH. Reconsidering anhedonia in depression: lessons from translational neuroscience. *Neurosci Biobehav Rev*. 2011;35(3):537–555.
21. Pizzagalli DA, Iosifescu D, Hallett LA, et al. Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task. *J Psychiatr Res*. 2008;43(1):76–87.
22. Yang X-H, Huang J, Zhu C-Y, et al. Motivational deficits in effort-based decision making in individuals with subsyndromal depression, first-episode and remitted depression patients. *Psychiatry Res*. 2014;220(3):874–882.
23. Pechtel P, Dutra SJ, Goetz EL, et al. Blunted reward responsiveness in remitted depression. *J Psychiatr Res*. 2013;47(12):1864–1869.
24. Phillips ML, Chase HW, Sheline YI, et al. Identifying predictors, moderators, and mediators of antidepressant response in major depressive disorder: neuroimaging approaches. *Am J Psychiatry*. 2015;172(2):124–138.
25. Leppänen JM. Emotional information processing in mood disorders: a review of behavioral and neuroimaging findings. *Curr Opin Psychiatry*. 2006;19(1):34–39.
26. Harmer CJ, Cowen PJ. 'It's the way that you look at it'—a cognitive neuropsychological account of SSRI action in depression. *Philos Trans R Soc Lond B Biol Sci*. 2013;368(1615):20120407.
27. Zimmerman M, Martinez J, Attiullah N, et al. How should residual symptoms be defined in depressed patients who have remitted? *Compr Psychiatry*. 2013;54(2):91–96.

Supplementary material follows this article.

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Supplementary Material

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List of Supplementary Material for the article

1. eTable 1 Medication details for depressed and remitted groups

Disclaimer

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Supplementary eTable 1. Medication details for depressed and remitted groups. Patients are sorted by incentive effect.

Patients (incentive effect)	Depressed group (length of treatment)	Patients (incentive effect)	Remitted group
1 (0.16)	Clomipramine (10)	1 (0.59)	Ø
2 (0.08)	Escitalopram (9)	2 (0.46)	Paroxetine 60 mg
3 (0.04)	Paroxetine (7)	3 (0.44)	Ø
4 (0.04)	Clomipramine (6)	4 (0.41)	Carbamazepine 400 mg
5 (0.05)	Fluoxetine (5)	5 (0.38)	Ø
6 (0.02)	Ø	6 (0.36)	Escitalopram 10 mg
7 (0.02)	Venlafaxine (8)	7 (0.22)	Clomipramine 25 mg
8 (0.01)	Ø	8 (0.16)	Venlafaxine 75 mg
9 (0.01)	Venlafaxine (3)	9 (0.15)	Fluoxetine 20 mg
10 (-0.01)	Seropram (3)	10 (0.12)	Ø
11 (-0.01)	Clomipramine (4)	11 (0.09)	Sertraline 100 mg, quetiapine 100 mg

12 (-0.01)	Flovoxamine (6)	12 (0.08)	Paroxetine 20 mg
13 (-0.01)	Clomipramine (4)	13 (0.08)	Escitalopram 10 mg
14 (-0.01)	Mirtazapine (2)	14 (0.08)	Escitalopram 20 mg
15 (-0.01)	Duloxetine (5)	15 (-0.00)	Ø
16 (-0.02)	Ø	16 (-0.01)	Fluoxetine 20 mg
17 (-0.03)	Iproniazide (10)	17 (-0.01)	Venlafaxine 150 mg
18 (-0.03)	Clomipramine (1)	18 (-0.03)	Lamotrigine 300 mg, aripiprazole 5 mg
19 (-0.01)	Venlafaxine (7)	19 (-0.04)	Venlafaxine 75 mg, carbamazepine 600, aripiprazole 5 mg
20 (-0.01)	Venlafaxine mirtazapine (12)	20 (-0.04)	Fluoxetine 20 mg
21 (-0.05)	Duloxetine (10)		
22 (-0.06)	Amitriptyline (4)		