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A multi-pronged investigation of option generation using depression, PET and modafinil

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Option generation is a critical process in decision making, but previous studies have largely focused on choices between options given by a researcher. Consequently, how we self-generate options for behaviour remain poorly understood. Here, we investigated option generation in major depressive disorder and how dopamine might modulate this process, as well as the effects of modafinil (a putative cognitive enhancer) on option generation in healthy individuals.

We first compared differences in self-generated options between healthy non-depressed adults [$n = 44$, age = 26.3 years (SD 5.9)] and patients with major depressive disorder [$n = 54$, age = 24.8 years (SD 7.4)]. In the second study, a subset of depressed individuals [$n = 22$, age = 25.6 years (SD 7.8)] underwent PET scans with ^{11}C-raclopride to examine the relationships between dopamine D_2/D_3 receptor availability and individual differences in option generation. Finally, a randomized, double-blind, placebo-controlled, three-way crossover study of modafinil (100 mg and 200 mg), was conducted in an independent sample of healthy people [$n = 19$, age = 23.2 years (SD 4.8)] to compare option generation under different doses of this drug.

The first study revealed that patients with major depressive disorder produced significantly fewer options [$t(96) = 2.68$, $P = 0.009$, Cohen's $d = 0.54$], albeit with greater uniqueness [$t(96) = -2.54$, $P = 0.01$, Cohen's $d = 0.52$], on the option generation task compared to healthy controls. In the second study, we found that ^{11}C-raclopride binding potential in the putamen was negatively correlated with fluency ($r = -0.69$, $P = 0.001$) but positively associated with uniqueness ($r = 0.59$, $P = 0.007$). Hence, depressed individuals with higher densities of unoccupied putamen D_2/D_3 receptors in the putamen generated fewer but more unique options, whereas patients with lower D_2/D_3 receptor availability were likely to produce a larger number of similar options. Finally, healthy participants were less unique [$F(2,36) = 3.32$, $P = 0.048$, partial $\eta^2 = 0.16$] and diverse [$F(2,36) = 4.31$, $P = 0.021$, partial $\eta^2 = 0.19$] after taking 200 mg versus 100 mg and 0 mg of modafinil, while fluency increased linearly with dosage at a trend level [$F(1,18) = 4.11$, $P = 0.058$, partial $\eta^2 = 0.19$].

Our results show, for the first time, that option generation is affected in clinical depression and that dopaminergic activity in the putamen of patients with major depressive disorder may play a key role in the self-generation of options. Modafinil was also found to influence option generation in healthy people by reducing the creativity of options produced.

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Abbreviations: BDI = Beck Depression Inventory II; BP_{ND} = non-displaceable binding potential; HAMD = Hamilton Rating Scale for Depression; MDD = major depressive disorder; SHAPS = Snaith Hamilton Pleasure Scale

Introduction

Option generation is a critical process in decision making.[1] The ability to generate potential options is important for accomplishing everyday tasks like 'what to eat for lunch' through to the wider creation of innovative technological solutions. Interestingly, the neuroscience of decision making has largely concentrated on choices between options given by a researcher.[2] Such forced choice situations are increasingly thought to be limited in ecological validity and, thus, some investigators have begun to focus on the more natural phenomenon of foraging—or how people decide between exploiting versus exploring their environments—instead.[3,4] Nevertheless, this work still assumes that behavioural options are already represented by an individual, which is not always true in the real world.[5,6]

Surprisingly little is known about self-generated behavioural choices.[5] To investigate this, Ang *et al.*[7] recently developed a novel behavioural paradigm and found that the process of option generation involves a trade-off between fluency (i.e. persistence in generating many options) and uniqueness (i.e. flexibility in producing novel options). Crucially, increasing levels of dopamine through specific pharmacological manipulations shifted the balance towards greater fluency but diminished uniqueness.[7] We aimed to build on these promising findings and advance our understanding in two important ways. First, we investigated the process of option generation in major depressive disorder (MDD) and how dopamine might modulate them. Our second objective was to examine whether modafinil, a putative cognitive enhancer, might influence the self-generation of options in healthy individuals.

MDD is a debilitating, recurrent and prevalent mental illness affecting more than 240 million people worldwide.[8] Emerging evidence suggest that depressed individuals are impaired at weighing the effort costs and rewards when selecting between possible options to act on.[1,9,10] The volitional generation of behavioural options, however, has never been investigated in patients with MDD—despite speculations that abnormalities in this process may contribute to apathy and anhedonia, the latter being a core symptom of MDD.[1,5] Findings from executive tests of verbal fluency, which require participants to produce as many words as possible within a phonemic or semantic category in a fixed time,[11,12] suggest that depression might be associated with deficits in the fluency of generating options.[13] Unfortunately, these tests are more generally considered to be assessments of executive functioning and processing speed, with outputs under clear instructions. Thus, it is unclear whether they are an appropriate measure of the ability to self-generate behavioural options. Moreover, performance on these tasks may be strongly influenced by an individual's linguistic ability, as well as educational and cultural background.[14–19] The discrete nature of words also makes it difficult to quantify creativity within the semantic space. Consequently, option generation in MDD remains unexplored.

Modafinil is a psychostimulant that helps promote wakefulness and is FDA-approved to treat excessive daytime sleepiness associated with narcolepsy and shift-work sleep disorder.[20–22] Numerous groups have reported that this drug improved cognitive functions such as attention, working memory, planning and prepotent response inhibition in animals,[23–29] healthy adults who were sleep-deprived[30–36] and non-sleep-deprived,[37–43] as well as clinical populations, including individuals with narcolepsy,[44,45] schizophrenia,[46–49] depression[50] and attention deficit hyperactive disorder.[51–53] Some recent studies have further suggested that while modafinil facilitates processes that support cognitive stability such as attention, it might at the same time reduce creative thinking in healthy people.[43,54] Given that option generation involves a trade-off between persistence in generating numerous options (i.e. fluency) and flexibility in producing novel options (i.e. uniqueness), this raises an important question of how modafinil might influence the self-generation of options in healthy people.

Here, the aforementioned questions were investigated in three studies with a simple measure of option generation that was quantitative, objective and culture-free.[7] First, we compared differences in self-generated options between healthy non-depressed adults (n = 44) and patients with MDD (n = 54) and hypothesized that the latter would have reduced fluency relative to the controls (Study 1). To further investigate whether dopamine might modulate option generation in depression, a subset of participants with MDD (n = 22) also underwent PET scans with ^{11}C-raclopride (a validated radioligand with high specificity and affinity for dopamine D_2/D_3 receptors).[55,56] We predicted that ^{11}C-raclopride binding potential in the striatum, which indexes dopamine D_2/D_3 receptor availability, would correlate with individual differences in fluency and uniqueness (Study 2). Finally, a randomized, double-blind, placebo-controlled, three-way crossover study of modafinil (100 mg and 200 mg) was conducted in an independent sample of healthy people (n = 19). This design allowed us to compare option generation performance when levels of modafinil differed within-subject, thereby permitting inferences to be made about the effects of modafinil. Based on evidence that modafinil improves cognitive stability but reduces creativity, we expected higher doses of modafinil to improve fluency but reduce the uniqueness of options generated (Study 3).

Materials and methods

Participants

The sample for Study 1 was composed of 44 healthy volunteers and 54 depressed patients (see Table 1 for demographics).

Table 1 Participant characteristics

	Study 1		Study 2	Study 3
	Healthy controls (n = 44)	MDD (n = 54)	MDD (n = 22)	Healthy controls (n = 19)
Age, years (SD)	26.3 (5.9)	24.8 (7.4)	25.6 (7.8)	23.2 (4.8)
Sex, n (%)[†]				
Female	31 (70.5)	30 (55.6)	11 (50.0)	8 (42.1)
Male	13 (29.5)	24 (44.4)	11 (50.0)	11 (57.9)
Race, n (%)				
White	25 (56.8)	35 (64.8)	17 (77.3)	10 (52.6)
African-American	7 (15.9)	8 (14.8)	3 (13.6)	0 (0.0)
Asian	9 (20.5)	8 (14.8)	0 (0.0)	9 (47.4)
Other	3 (6.8)	3 (5.6)	2 (9.1)	0 (0.0)
Ethnicity, n (%)				
Hispanic	9 (20.5)	8 (14.8)	3 (13.6)	2 (10.5)
Non-Hispanic	35 (79.5)	46 (85.2)	19 (86.4)	17 (89.5)
Antidepressants, n (%)				
Yes	–	12 (22.2)[a]	0 (0)	–
No	–	42 (77.8)	22 (100)	–
Education, years (SD)	16.4 (3.6)	15.0 (2.4)	15.1 (1.3)	16.0 (3.0)
HAMD (SD)[***]	0.6 (1.2)	15.0 (7.3)	18.9 (4.2)	0.2 (0.5)
SHAPS (SD)[***]	20.0 (6.1)	30.6 (6.0)	32.2 (5.0)	18.5 (3.7)
BDI				
Total (SD)[***]	1.7 (3.0)	27.7 (9.5)	–	–
Cognitive (SD)[***]	0.6 (1.1)	12.1 (4.2)	–	–
Somatic-Affective (SD)[***]	1.1 (2.3)	15.6 (6.5)	–	–
Apathy evaluation scale (SD)[***]	65.6 (5.4)	49.5 (9.8)	–	–

***$P < 0.001$.

†$P < 0.10$. Symbols indicate variables that are different between patients with MDD and healthy controls in Study 1.

aNine patients were on selective-serotonin reuptake inhibitors (SSRIs), two were on serotonin-norepinephrine reuptake inhibitors (SNRIs) and one was on SNRIs and serotonin receptor antagonists and reuptake inhibitors (SARIs).

Forty-eight patients were recruited from the Boston metropolitan area and met the Structured Clinical Interview for DSM-IV-TR criteria for MDD; six inpatients were recruited from the Short Term Unit at McLean Hospital and had a primary diagnosis of MDD. Exclusion criteria for patients were history of psychosis or bipolar disorder, substance-related disorders, active suicidality, lifetime history of electroconvulsive therapy or unstable medical conditions. All healthy individuals were recruited from the Boston metropolitan area and completed the Structured Clinical Interview for DSM-IV-TR to confirm the absence of current or history of psychiatric illnesses. The study was approved by the Partners Human Research Committee. After providing written informed consent, participants completed the option generation task in a quiet, dimly-lit room.

Twenty-two patients who were recruited from the community in Study 1 also took part in Study 2 (Table 1). These participants were part of a larger study investigating the neurobiological mechanisms of placebo in depression; they underwent a dynamic PET scan with ^{11}C-raclopride after completing the option generation task at the baseline session (i.e. before any study drug had been administered).

In Study 3, an independent sample of 19 healthy volunteers (Table 1) was recruited from the Boston metropolitan area and completed the Structured Clinical Interview for DSM-IV-TR to confirm the absence of current or past psychiatric illnesses. They were tested using a randomized, double-blind, placebo-controlled, three-way crossover design with modafinil (100 mg and 200 mg) as part of a larger study examining links between modafinil and electrophysiological correlates of cognitive control. These doses of modafinil were chosen based on previous EEG studies showing an enhancement of oscillatory power associated with high-control rule selection in the theta, beta and alpha ranges during a cognitive control task.[57,58] The option generation task was administered after participants completed two separate cognitive control tasks. All participants gave written informed consent and the study was approved by the Mass General Brigham Human Research Committee.

Option generation task

This paradigm was programmed with PsychToolBox on MATLAB (MathWorks) and administered on a 13.5″ Microsoft Surface touchscreen laptop with a screen resolution of 2256 × 1504 at a 60 Hz frame rate, width of 285 mm and height of 190 mm. The task displayed two red circles (each of radius 10 mm) that were vertically aligned in the middle of the screen and separated by a distance of 114 mm (Fig. 1A). Participants were required to 'Draw as many and as different paths as you can from the bottom red circle to the top red circle in 1.5 minutes'. Lines appeared in real-time as subjects drew them. Drawn paths were allowed to intersect and stayed visible throughout the task in order to minimize the load on working memory. There were three metrics of interest, namely fluency, uniqueness and diversity. We assessed fluency by the total number of paths generated.

Quantifying uniqueness and diversity

To quantify uniqueness, every path option i was denoted as a set of coordinates $x_i(t)$, $y_i(t)$ for each time step of the path. First, we re-sampled every path at 200 points along the path, as a function of distance along the path. This was done by computing distance along the path as $s_i(t) = \sum_{\tau=1}^{t} \left\| \begin{bmatrix} x_i(\tau)-x_i(\tau-1) \\ y_i(\tau)-y_i(\tau-1) \end{bmatrix} \right\|$ and using linear interpolation along $s(t)$ to compute a new vector of coordinates $\mathbf{h}_i(s)$. To capture other features of the trajectory's shape (e.g. sharp corners or smooth curves), we also included the first

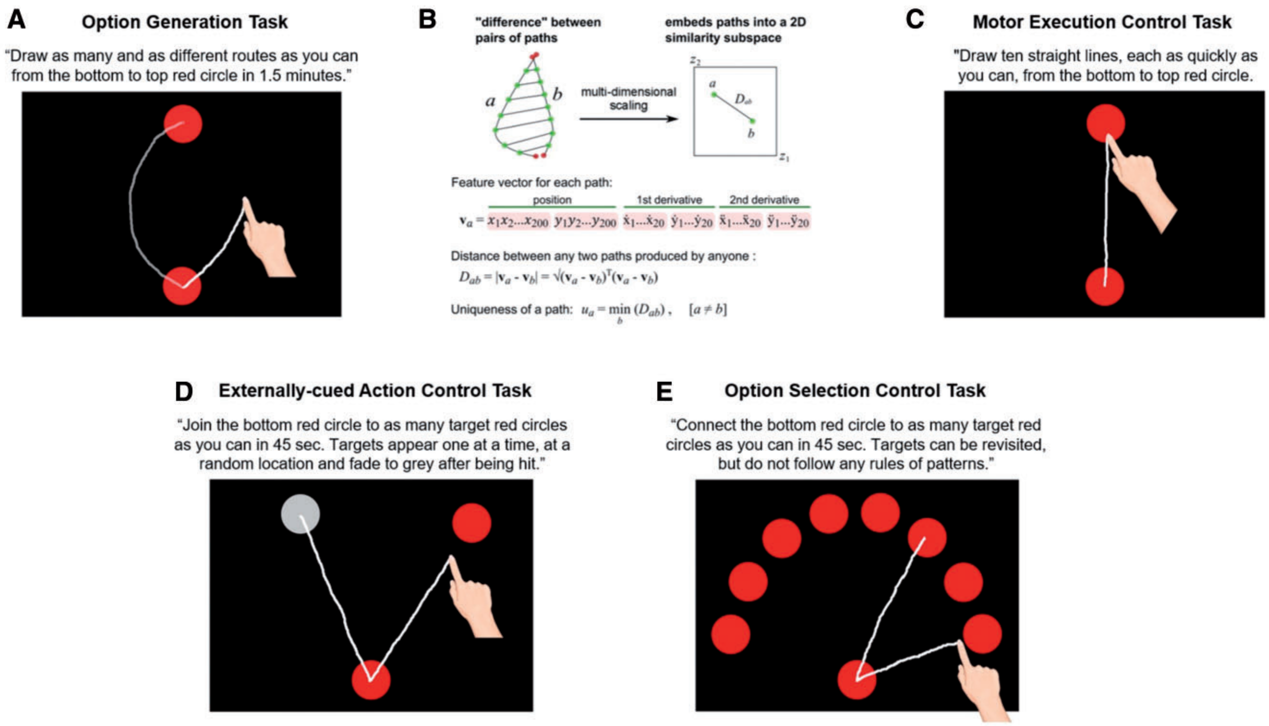

Figure 1 Paradigms and quantitfication of uniqueness and diversity. (**A**) Option generation task. Participants were given 1.5 min to draw as many and as different paths as they could between two fixed red circles on a touchscreen computer. (**B**) Quantifying uniqueness and diversity. Each path was divided into 200 points equally spaced along its length in order to derive a feature vector that comprised the position, first derivatives (which accounted for slopes) and second derivatives (which accounted for curvatures). The 'distance' between any two paths was computed by subtracting the features of one path from the other; and the uniqueness of each path generated by every participant was then taken to be the 'distance' between it and the most similar path produced by all other subjects in the three studies of this paper. Multi-dimensional scaling was also used to project the pairwise distance matrix of every participant onto a 2D subspace, and diversity was approximated by the area of the convex hull covering these points. (**C**) Motor execution control task. To assess baseline drawing speed, participants were asked to produce 10 straight lines, each as quickly as they could, between the two fixed circles. (**D**) Externally-cued action control task. To account for motor planning, participants were required to draw a straight line from the bottom red circle to a random target location decided by the computer. A new target location was presented after the completion of each path, and subjects had to connect to as many target locations as possible in 45 s. (**E**) Option selection control task. To assess option selection ability, participants were required to choose an option from a set of displayed target locations and then draw a straight line from a central start location to it. The goal was to make as many connections as possible in 45 s. Figure modified from Ang *et al.*[7]

derivative $\dot{\mathbf{h}} = \mathbf{h}(s) - \mathbf{h}(s-1)$ to account for slopes and second derivative $\ddot{\mathbf{h}}$ to account for curvatures. Hence, the feature vector $\mathbf{v}$ for each path was written as $\mathbf{v}_i = \left[\mathbf{h}_x, \mathbf{h}_y, \dot{\mathbf{h}}_x, \dot{\mathbf{h}}_y, \ddot{\mathbf{h}}_x, \ddot{\mathbf{h}}_y\right]$. The difference between any pair of paths $d_{ij} = |\mathbf{v}_i - \mathbf{v}_j|$ quantified how different the features of one path was from the other. To account for left-right mirror similarity, we also computed the difference d'_{ij} using the mirror-image path (i.e. transforming $\mathbf{h}_x \rightarrow -\mathbf{h}_x$ and the associated derivatives) and used $\min\left(d_{ij}, d'_{ij}\right)$ as the difference metric. The uniqueness of a path was then defined as the smallest difference between that path and any other path generated by any subject in all three studies: $u_i = \min_j (d_{ij}) [i \neq j]$. Hence, the larger u_i is, the more dissimilar that particular path is compared with any other generated path (Fig. 1B).

Multidimensional scaling was also applied on the pairwise distance matrix for each participant by using the default fitting algorithm with a metric stress criterion in MATLAB. Every path was assigned a 2D coordinate such that the difference metric between every pair of paths matched as closely as possible the distance between the corresponding points in the 2D space. Diversity was then approximated by the area of the convex hull covering these points.

Control tasks

Three control tasks that were closely-matched to the option generation task were also administered to account for possible confounds.

Motor execution control task

First, options might have been generated but not produced due to slower drawing speed. To account for this, a motor execution control task was administered before the option generation task. Two red circles (as in the option generation task) were displayed and subjects had to 'Draw ten straight lines, each as quickly as you can, from the bottom red circle to the top red circle' (Fig. 1C). Lines appeared in real-time as participants drew them and were erased from the screen between movements. The measure of interest was the average time taken to draw each line (excluding time between lines).

Externally-cued action control task

Next, participants might have generated options but not produced them due to motor planning deficits. An externally-cued action control task was utilized to account for this. Subjects were instructed to 'Join the bottom red circle to as many target red circles as you can in 45 seconds. Targets appear one at a time, at a random location, and fade to grey after being hit' (Fig. 1D). Lines appeared in real-time as they were drawn. Unbeknownst to participants, targets always appeared at a distance of 114 mm (i.e. the distance between the two red circles in the option generation task) from the starting point but at a random angle that ranged between ±90°. Hence, this task required a different motor plan for each path, but subjects did not have to generate any options for the next action as this was given by the computer.

Option selection control task

Finally, an individual might have conceived of many path options, but had difficulty choosing which of them to draw. To account for this, an *option selection control task* was employed. This task presented subjects with 24 red targets that were spaced equally along an arc (Fig. 1E). Each target appeared at a distance of 114 mm (i.e. the distance between the two red circles in the option generation task) from the bottom red circle and participants were told to 'Connect the bottom red circle to as many target red circles as you can in 45 seconds. Targets can be revisited, but do not follow any rules or patterns'. Lines appeared in real-time as they were drawn. Hence, each movement required the individual to select an option, but there was no need to generate unique paths.

Clinical assessments

The Snaith Hamilton Pleasure Scale (SHAPS)[59] is a 14-item self-report measure that assesses consummatory anhedonia. Each item was scored on a four-point Likert scale and a higher total score indicates a greater inability to experience pleasure. The Hamilton Rating Scale for Depression (HAMD)[60] is a 17-item clinician-administered scale that assesses the severity of depression. Each item relates to a symptom of depression experienced over the past week and higher scores indicate greater severity. All participants in Study 1 completed the SHAPS and HAMD.

The Apathy Evaluation Scale (AES)[61] is an 18-item self-report measure of motivation. Each item is scored on a four-point Likert scale and a higher total score indicates greater levels of motivation. A subset of 43 healthy controls and 25 patients with MDD in Study 1 who did not participate in the PET study completed the AES. The Beck Depression Inventory II (BDI)[62] is a 21-item scale that measures the severity of depression. Each item relates to a symptom of depression, e.g. hopelessness, and is scored on a four-point Likert scale. There are two standard subscales, namely cognitive and somatic-affective, and a higher total and subscale score indicates greater symptom severity. A subset of 42 healthy controls and 25 patients with MDD in Study 1 completed the BDI.

PET imaging procedures

Subjects were part of a larger ongoing study investigating the neurobiological underpinnings of placebo in depression. Neuroimaging included a dynamic ^{11}C-raclopride PET scan, during which a reward task was administered to induce dopamine release; however, the present analysis focused on the baseline portion of the scan (i.e. prior to reward task onset) to estimate the non-displaceable binding potential (BP_{ND}) of ^{11}C-raclopride, reflecting baseline level of D_2/D_3 receptor availability.

Study participants were scanned dynamically for up to 90 min on a whole-body integrated PET/MR scanner (Siemens Biograph mMR) installed at Massachusetts General Hospital's Martinos Center for Biomedical Imaging, following an intravenous bolus injection of ^{11}C-raclopride [injected dose: 13.3 ± 2.3 mCi, (mean ± SD)]. A structural MRI scan was acquired for each participant at the beginning of the imaging study using a 3D T_1-weighted multi-echo magnetization prepared rapid gradient echo sequence with the following parameters[63]: repetition time = 2530 ms, echo times = 1.69, 3.55, 5.41, 7.27 ms, inversion time = 1100 ms, matrix size = $256 \times 256 \times 176$ and voxel size = $1 \times 1 \times 1$ mm^3. The structural MRI scan was used to generate an attenuation map for PET using a previously validated hybrid segmentation and an atlas-based approach.[64]

PET data analysis

Dynamic list-mode PET data corresponding to the first hour of scanning were binned into temporal frames of up to 1 min and reconstructed and corrected for motion using the following multi-step approach. First, an initial dynamic reconstruction was performed without including attenuation correction, followed by application of spatial Gaussian smoothing [6-mm full-width at half-maximum (FWHM)] to each frame and rigid-body registration of the activity volume for each frame to a selected reference frame. The attenuation map was then registered to the resulting time-averaged volume and transformed using the registration transformations obtained in the first step, yielding an attenuation map for each frame. Second, another dynamic reconstruction was performed, which included the frame-dependent attenuation map obtained in the first step and standard corrections for dead-times, random and scattered coincidences. Note that the attenuation map used during reconstruction also accounted for 'static' attenuating media such as the scanner's bed and the MRI head coil. Third, activity volumes were smoothed with a 4-mm FWHM Gaussian filter and rigidly registered to a reference frame, followed by another registration to the resulting time-averaged volume. All PET reconstructions were performed using OP-OSEM 3D with three iterations and 21 subsets on a $344 \times 344 \times 127$ array with voxel size $2.08 \times 2.08 \times 2.03$ mm^3. Image registrations were performed using FMRIB's linear image registration tool (FLIRT; FMRIB Software Library, University of Oxford, UK) with normalized mutual information as the data consistency criterion and six degrees of freedom.

Afterward, the structural MRI scan for each subject was rigidly aligned to PET space using FLIRT, followed by non-rigid registration of the Montreal Neurological Institute (MNI) T_1-weighted template to MNI space using FMRIB's non-linear image registration tool (FNIRT). Regions of interest were defined in MNI space using the Harvard-Oxford structural atlas available with the FMRIB Software Library for the following bilateral regions: caudate nucleus, putamen and nucleus accumbens, as well as the cerebellum (excluding the vermis). The region of interest masks were then transformed to MNI space using the subject-specific deformation field, and activity concentration histories were extracted for the selected regions. The linear parametric neurotransmitter PET model[65] was fitted to regional time-activity curves to simultaneously estimate the baseline [i.e. prior to MID (Monetary Incentive Delay) task onset] ^{11}C-raclopride non-displaceable binding potential (BP_{ND}) as well as MID task-induced neurotransmitter release using the cerebellum as reference (see Supplementary material for details). Only the BP_{ND} results were included in this study. Analyses of the PET data were performed blind to the option generation data.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Results

Depressed patients were less fluent but more unique than healthy controls

The option generation paradigm was first administered to a group of 44 healthy controls and 54 patients with MDD (Study 1). There were no group differences in performance on the three control tasks [motor execution: $t(96) = 1.06$, $P = 0.29$; externally-cued action: $t(96) = 1.31$, $P = 0.19$; option selection: $t(96) = 1.01$, $P = 0.32$]. Nevertheless, we accounted for the control tasks and found a significant negative correlation between fluency and uniqueness (r = –0.70, $P < 0.001$) and fluency and diversity (r = –0.51, $P < 0.001$), as well as positive correlation between uniqueness and diversity (r = 0.79, $P < 0.001$). Results were similar even without accounting for the control tasks (fluency-uniqueness: r = –0.59, $P < 0.001$; fluency-diversity: r = –0.33, P = 0.001; uniqueness-diversity: r = 0.79, $P < 0.001$). These findings replicate a prior study[7] and suggest that there was a natural trade-off between fluency and creativity; that is, people tended to generate either many similar options or fewer unique paths.

Independent-samples t-tests revealed a significant effect of group (MDD versus healthy controls) on option generation (after regressing out performance on control tasks). Specifically, patients with MDD had lower fluency compared to the healthy controls [$t(96)$ = 2.68, P = 0.009, Cohen's d = 0.54; Fig. 2A], but they exhibited greater uniqueness in their generated paths [$t(96)$ = –2.54, P = 0.01, Cohen's d = 0.52; Fig. 2B]. This suggests that the depressed individuals were biased towards generating fewer options but with higher mean uniqueness. There was no significant group difference in diversity [$t(96)$ = –1.32, P = 0.19, Cohen's d = 0.27; Fig. 2C], indicating that the options produced by healthy controls and patients with MDD were similarly varied. The results were confirmed when excluding depressed participants who were on medication [fluency: $t(84)$ = 2.36, P = 0.02, Cohen's d = 0.51; uniqueness: $t(84)$ = –2.23, P = 0.03, Cohen's d = 0.48; diversity: $t(84)$ = –1.11, P = 0.27, Cohen's d = 0.24]. Because of a trending group difference in gender proportions [$\chi^2(1,98)$ = 2.87, P = 0.09], we ran separate analyses that additionally accounted for the effects of gender as a between-subjects factor and verified that similar findings were obtained. Specifically, there was a significant main effect of group for fluency [$F(1,94)$ = 10.1, P = 0.002, partial η^2 = 0.097] and uniqueness [$F(1,94)$ = 6.95, P = 0.01, partial η^2 = 0.069] but not diversity [$F(1,94)$ = 1.67, P = 0.20, partial η^2 = 0.017]. In contrast, the group × gender interaction was not significant for fluency, uniqueness or diversity (all P-values were $>$0.29).

There was no difference in the total path length between patients with MDD and healthy controls [$t(96)$ = –0.97, P = 0.33, Cohen's d = 0.20], suggesting that both groups drew similar lengths of paths. However, the mean path length for the patients with MDD was longer than that for healthy controls [$t(96)$ = –2.12, P = 0.037, Cohen's d = 0.43]. There was also no group difference in the average planning time (i.e. time paused between paths) [$t(96)$ = –0.79, P = 0.44, Cohen's d = 0.16], which indicated that depressed individuals and healthy volunteers took similar amounts of time to think of each path.

We additionally investigated whether levels of self-reported motivation (based on the AES) in MDD might be associated with option generation and found a trending correlation with fluency (r = 0.36, P = 0.075), suggesting that depressed individuals who were more motivated came up with more options. In contrast, there was no association between motivation and uniqueness (r = –0.23, P = 0.26) or diversity (r = –0.22, P = 0.29). Within the MDD group, option generation was also not correlated with anhedonia based on the SHAPS (fluency: r = 0.03, P = 0.86; uniqueness: r = –0.10, P = 0.48; diversity: r = 0.07, P = 0.60), depression severity based on the HAMD total score (fluency: r = 0.12, P = 0.44; uniqueness: r = –0.06, P = 0.68; diversity: r = –0.09, P = 0.57) and BDI total score (fluency: r = 0.21, P = 0.32; uniqueness: r = 0.14, P = 0.49; diversity: r = 0.01, P = 0.95), as well as the BDI cognitive (fluency: r = 0.14, P = 0.51; uniqueness: r = 0.03, P = 0.90; diversity: r = –0.08, P = 0.71) and somatic-affective symptom subscores (fluency: r = 0.21, P = 0.31; uniqueness: r = 0.19, P = 0.36; diversity: r = 0.07, P = 0.74).

Putamen D_2/D_3 receptor availability was associated with option generation

To investigate the relationship between striatal dopamine function and self-generated behavioural options, we conducted ^{11}C-raclopride PET scans on a subset of 22 patients with MDD after the option generation task (Study 2). One subject exited the scanner early while the data for two participants could not be processed; hence, the final PET sample size was n = 19. Consistent with previous reports,[66–70] we found that in some striatal regions, there were significant associations between the BP_{ND} and age ($r_{caudate}$ = –0.70, P = 0.001; $r_{putamen}$ = –0.61, P = 0.006; $r_{accumbens}$ = –0.22, P = 0.37), as well as larger BP_{ND} in females compared with males [$t_{accumbens}(17)$ = –2.98, P = 0.008; $t_{caudate}(17)$ = –1.67, P = 0.11; $t_{putamen}(17)$ = –2.03, P = 0.06]. Thus, age and gender were partialled out from BP_{ND} in all three subregions in subsequent analyses. We also regressed performance on the control tasks from the option generation metrics.

Among the subjects with MDD participating in the PET study, the BP_{ND} in the putamen was negatively correlated with fluency (r = –0.69, P = 0.001) but positively associated with uniqueness (r = 0.59, P = 0.007) and related at a trend level to diversity (r = 0.43, P = 0.066; Fig. 3). This suggests that individuals with higher

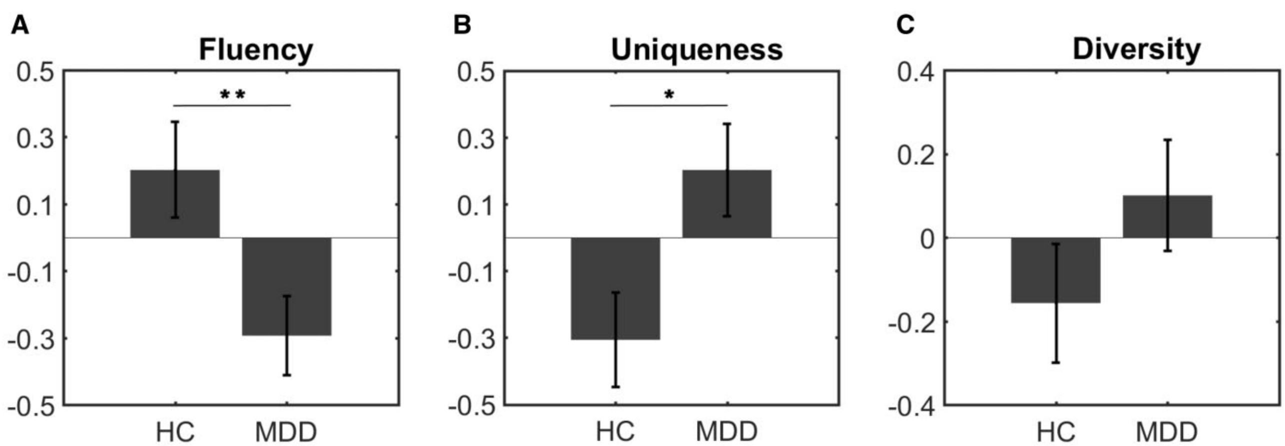

Figure 2 Comparison of (A) fluency, (B) uniqueness and (C) diversity between healthy controls (HC) and patients with MDD. After accounting for performance on three controls tasks, the patients with MDD were found to have generated significantly fewer options compared with the HCs. However, they exhibited greater uniqueness in the paths produced, suggesting that the depressed patients were biased towards generating fewer options but with higher mean uniqueness. There was no difference in diversity, indicating that the options produced by both groups were similarly varied. **$P < 0.01$, *$P < 0.05$.

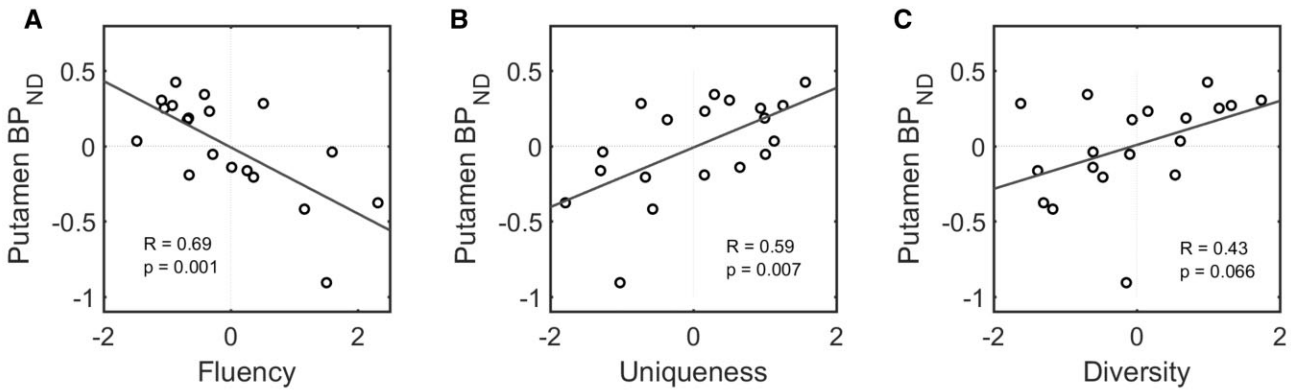

Figure 3 Correlation between putamen D_2/D_3 receptor availability and (A) fluency, (B) uniqueness as well as (C) diversity in patients with MDD. Putamen D_2/D_3 receptor availability, as indexed by ^{11}C-raclopride BP_{ND}, was negatively associated with fluency but positively correlated with uniqueness. There was also a positive trending relationship between putamen D_2/D_3 receptor availability and diversity. Note that age and gender have been regressed out from BP_{ND}. Performance on the control tasks have also been partialled out from the option generation metrics.

densities of unoccupied putamen D_2/D_3 receptors generated fewer but more unique options, while people with lower D_2/D_3 receptor availability were likely to produce a larger number of similar options. However, there was no significant relationship between the option generation metrics and BP_{ND} in the accumbens (fluency: r = –0.40, P = 0.09; uniqueness: r = 0.39, P = 0.10; diversity: r = 0.13, P = 0.60), or caudate BP_{ND} (fluency: r = –0.42, P = 0.08; uniqueness: r = 0.37, P = 0.12; diversity: r = 0.38, P = 0.11).

Steiger's tests found that the putamen-fluency correlation was significantly different from accumbens-fluency (z = –2.29, P = 0.02) and caudate-fluency (z = –2.55, P = 0.01), suggesting that the relationship between D_2/D_3 receptor availability and number of options generated was specific to the putamen. However, there was no statistical difference for putamen-uniqueness versus accumbens-uniqueness (z = 1.44, P = 0.15) and putamen-diversity versus caudate-diversity (z = 0.36, P = 0.72), and there was a trending difference for putamen-uniqueness versus caudate-uniqueness (z = –1.85, P = 0.06) as well as putamen-diversity versus accumbens-diversity (z = 1.96, P = 0.05).

Effects of modafinil on option generation

To determine how the cognitive enhancer modafinil might affect creativity and fluency in generating options, an independent sample of 19 healthy individuals was tested on three different doses of modafinil—0 mg, 100 mg and 200 mg—in a randomized, placebo-controlled, double-blind crossover experiment (Study 3). After controlling for performance on the control tasks, a repeated-measures ANOVA revealed no significant effect of dose on fluency [$F(2,36)$ = 1.82, P = 0.18, partial η^2 = 0.092]. However, there was trending evidence that the number of options generated increased linearly with dosage [$F(1,18)$ = 4.11, P = 0.058, partial η^2 = 0.19; Fig. 4A].

In contrast, we observed a significant effect of dose on uniqueness [$F(2,36)$ = 3.32, P = 0.048, partial η^2 = 0.16; Fig. 4B] and diversity [$F(2,36)$ = 4.31, P = 0.021, partial η^2 = 0.19; Fig. 4C]. *Post hoc* Bonferroni-corrected analyses found that participants generated less unique and less varied options after taking 200 mg of modafinil compared with placebo (uniqueness: P = 0.006; diversity: P = 0.010) and 100 mg (uniqueness: P = 0.083; diversity: P = 0.020). There was also evidence for a linear decrease in uniqueness [$F(1,18)$ = 9.48, P = 0.008, partial η^2 = 0.35] and diversity [$F(1,18)$ = 8.38, P = 0.010, partial η^2 = 0.32] as dosage increased. Crucially, we did not find any effect of repeated testing (i.e. session) on fluency [$F(2,36)$ = 0.16, P = 0.85, partial η^2 = 0.009], uniqueness [$F(2,36)$ = 0.04, P = 0.96, partial η^2 = 0.002] and diversity [$F(2,36)$ = 0.46, P = 0.64, partial η^2 = 0.025].

Discussion

The field of option generation is in its infancy. Ang and coworkers recently developed a behavioural paradigm to probe this process and found that option generation involves a trade-off between fluency and uniqueness. These researchers also showed that higher levels of dopamine increased the number of options produced but at the expense of reduced creativity.[7] Here, we built on these results by conducting a multi-pronged investigation to explore the influence of depression, striatal D_2 receptor characteristics, as well as modafinil, on option generation.

In the first study, we observed that patients with MDD (n = 54) produced significantly fewer options, albeit with greater uniqueness, on the option generation task compared with healthy controls (n = 44). Importantly, the lower levels of fluency in depression cannot be attributed to impairments in movement speed or motor execution, in planning or initiating actions or in selecting among generated options, as these factors were accounted for with three closely-matched control tasks. There were also no group differences in performance on the control tasks, and patients with MDD made longer paths on average compared with healthy volunteers. One speculation on the interpretation of our findings is that once a movement has begun, the patients are not motivated to complete the movement and, thus, rove or meander more. From this perspective, their primary 'deficit' might be considered to be the ability to maintain the end point as a goal. This leads to more unique movements when the goal has to be maintained (as in the option generation task) but normal performance when the movements must go immediately to the target (as in the control tasks). In this context, creativity might require some degree of 'release' from goal-driven behaviour. This is consistent with the wider literature implicating a lack of goal-directed behaviour in depression.[71]

Interestingly, option generation performance in the depressed participants did not correlate with the cognitive and somatic-affective subscales of the BDI, suggesting that the ability to generate options did not associate with these symptom dimensions in MDD. Moreover, although it has recently been suggested that deficits in option generation might contribute to apathy and anhedonia across a variety of neurological and psychiatric disorders including MDD,[1] we did not find any significant correlations between metrics on the option generation task and a self-report measure of consummatory anhedonia (SHAPS) in patients with

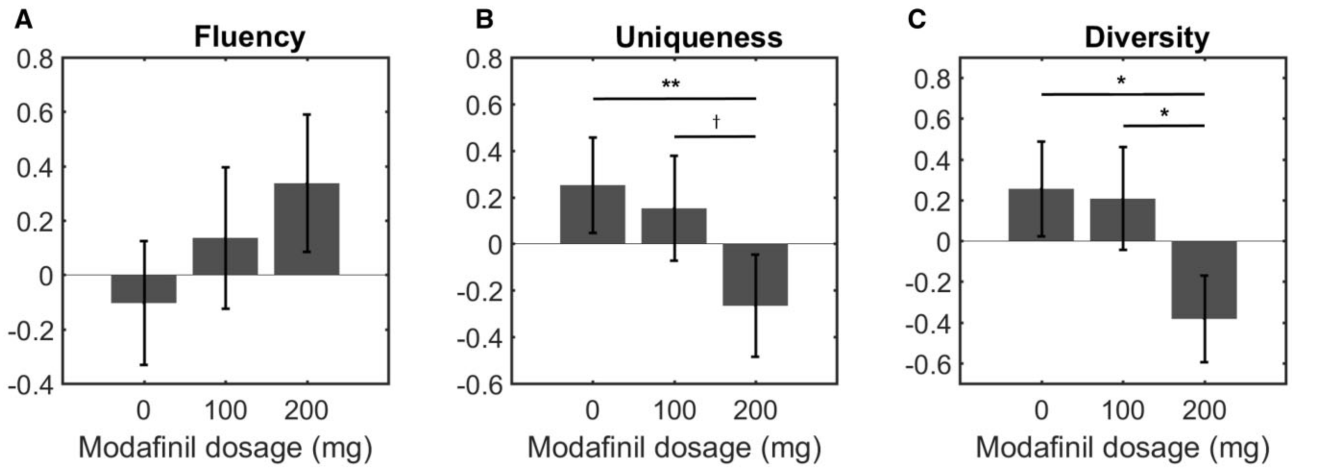

Figure 4 Comparison of (A) fluency, (B) uniqueness and (C) diversity between healthy volunteers on placebo, 100 mg and 200 mg of modafinil. After controlling for performance on the control tasks, there was no significant effect of dose on fluency. However, participants generated less unique and less varied options after taking 200 mg of modafinil compared with placebo and 100 mg of modafinil. $^{**}P < 0.01$, $^{*}P < 0.05$, $^{\dagger}P < 0.10$.

MDD and healthy controls. It is possible that difficulty in generating options might contribute more specifically to dysfunctions in motivation (i.e. apathy), rather than the inability to experience pleasure. In support of this, we found that depressed patients who reported greater levels of motivation (based on the apathy evaluation scale) also tended to generate more options, albeit at a trend level in a relatively small sample. This finding is interesting, because apathy is typically framed in terms of deficits in evaluating options, but our results tentatively suggest that impairments in the ability to self-generate possible options for action may also contribute to a lack of motivation to act.[72] An important avenue for future research will be to examine the relationship between option generation and apathy in a larger cohort of patients with MDD.

Our second study examined whether dopamine might modulate option generation in depression via PET scans with ^{11}C-raclopride in a subset of participants with MDD from the first study. By analysing the BP_{ND} (which refers to the ratio between bound and unbound raclopride molecules and reflects the number of D_2/D_3 receptor sites available for additional binding), it was observed that individuals with MDD who had greater D_2/D_3 receptor availability in the putamen generated fewer but more unique paths, whereas depressed individuals with lower BP_{ND} were more likely to produce a larger number of similar options. This suggests that individual differences in putamen D_2 receptor availability are associated with variations in option generation in depression. One interpretation of these findings is that patients with MDD and higher endogenous levels of dopamine were more likely to exhibit greater fluency but lower uniqueness during option generation. This was consistent with a prior study, which showed that the drug-induced dopamine increase in Parkinson's disease and healthy people led to the production of more options with lower uniqueness.[7] However, the functional meaning of BP_{ND} is still under debate; it is also possible that BP_{ND} reflects differences in receptor regulation and/or ligand affinity.[73] Interestingly, fluency was specifically correlated to BP_{ND} in the putamen but not the caudate or accumbens. This might not be surprising in light of substantial evidence implicating the putamen in the regulation of movement planning and execution.[74–77] However, we carefully controlled for individual differences in motor planning and execution ability with the use of control tasks that were closely matched to the option generation task. This suggests that dopaminergic activity in the putamen may be specifically involved in the generation of options, which is consistent with a growing body of evidence suggesting that the putamen contributes to a variety of cognitive functions such as working memory, reinforcement learning and language.[78–84]

Third, numerous studies have found that modafinil enhances performance in various cognitive domains, including attention, working memory, planning and prepotent response inhibition.[23–53] However, the effects on option generation remained unknown. We conducted the first study to investigate this and found that healthy people produced options that were significantly less unique and diverse after taking 200 mg of modafinil compared to 100 mg of modafinil as well as placebo. Interestingly, there was no significant difference in fluency (although a trending effect of fluency increasing linearly with increase in dosage was observed). These results suggest that modafinil reduced the creativity of options generated but did not affect the quantity of output. In other words, the reduction in creativity is not simply because of its effects on the fluency-uniqueness trade-off. This finding is in-line with a previous study showing that modafinil lowered performance on divergent thinking tasks in healthy individuals.[54] Nevertheless, these results should not be interpreted as evidence that modafinil does not affect fluency due to the trending effect and relatively small sample size, which might have insufficient statistical power to detect a significant effect on fluency. An alternative interpretation is that modafinil acts to increase focus and persistence at the expense of reducing flexible thinking. Hence, subjects were biased towards generating more options with less creativity. This interpretation would be consistent with recent studies showing that modafinil facilitates processes supporting cognitive stability but reduces creative thinking at the same time.[43,54] Future studies could seek to clarify this in a larger group of participants.

Unfortunately, the neurobiological mechanisms through which modafinil influences option generation is unclear. Studies have shown that modafinil blocks dopamine transporters and increases extracellular dopamine levels,[85–91] which would be in line with the finding from Ang *et al.*[7] that dopamine modulates option generation for behaviour. However, substantial evidence also suggests that modafinil has a complex neurochemical profile with primary effects on dopamine and norepinephrine, as well as effects on serotonin, gamma amino-butyric acid, glutamate, orexin and histamine that may be secondary to the catecholamine effects.[92] A potential avenue for future research could be to investigate whether other neurotransmitters might also impact on the self-generation of options in humans.

Limitations of this paper should be acknowledged. First, both the PET and modafinil samples were relatively small. Hence, results from these studies should be considered preliminary and await independent replication in larger samples. Second, the participants in these studies were relatively young adults and, thus, it is unclear whether findings will be similar for older adults or in children. Third, it is unclear whether the relationship between dopamine binding capacity and option generation in Study 2 is specific to MDD as healthy controls were not included.

In conclusion, option generation is an essential component of decision-making in humans, yet it is sparsely studied and poorly understood. We showed, for the first time, that this important process is affected in depressed patients and provided PET evidence suggesting that, within an MDD sample, dopaminergic activity in the putamen may play a key role in the self-generation of options. Our findings also indicate that modafinil, a putative cognitive enhancer, impacted this process in healthy people by reducing the creativity of options produced.

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Competing interests

Over the past 3 years, D.A.P. has received consulting fees from Albright Stonebridge Group, BlackThorn Therapeutics, Boehringer Ingelheim, Compass Pathway, Concert Pharmaceuticals, Engrail Therapeutics, Neurocrine Biosciences, Otsuka Pharmaceuticals, and Takeda Pharmaceuticals; one honorarium from Alkermes; and research funding from NIMH, Dana Foundation, Brain and Behavior Research Foundation, and Millennium Pharmaceuticals. In addition, he has received stock options from BlackThorn Therapeutics. J.H. is founder and a board observer of Eikonizo Therapeutics Inc.; on the scientific advisory board and a consultant for Delix Therapeutics, Psy Therapeutics and Fuzionaire Diagnostics; a consultant for Sanofi-Aventis, FogPharma, Velox Therapeutics, Amathus Therapeutics, Alkermes, Evolo Biosciences, Denali Therapeutics, Rodin Therapeutics, Vaccinex and SV Life Sciences; has sponsored research and license agreement from Expesicor; has sponsored research from Atai Life Sciences; and had the following paid positions or honoraria in non-profits outside Massachusetts General Hospital: ADDF advisor and grant reviewer, MIT LinQ Catalyst, American Chemical Society, NYU, Memorial Sloan Kettering, McGill University, NIH, Emory University, American Chinese Medical Exchange Society. Over the past 3 years, M.F. has received Research Support from: Acadia Pharmaceuticals, Aditum Bio Management Company, LLC, Allergan, Alkermes, Inc., Altimate Health Corporation, Angelini S.p.A, Aptinyx, Arbor Pharmaceuticals, LLC, Avanir Pharmaceuticals Inc., Axsome, Benckiser Pharmaceuticals, Inc., BioClinica, Inc, Biogen, BioHaven, Cambridge Science Corporation, Cerecor, Gate Neurosciences, Inc., GenOmind, LLC, Gentelon, LLC, Happify, Johnson & Johnson, Lundbeck Inc., Marinus Pharmaceuticals, Methylation Sciences, Inc., Millennium Pharmaceutics, Inc. Minerva Neurosciences, Neuralstem, NeuroRX Inc., Novartis, Otsuka, Pfizer, Premiere Research International, Protagenic Therapeutics, Inc., Relmada Therapeutics Inc., Reckitt, Shenox Pharmaceuticals, Stanley Medical Research Institute (SMRI), Taisho, Takeda, University of Michigan, Vistagen, National Institute of Drug Abuse (NIDA); National Institutes of Health (NIH), National Institute of Mental Health (NIMH), and PCORI. Speaking/Publishing: Lecture given at Global Medical Education Inc. Mood Disorders Summit, November 2020. Equity Holdings: Compellis; Psy Therapeutics. Royalty/patent, other income: Patents for Sequential Parallel Comparison Design (SPCD), licensed by MGH to Pharmaceutical Product Development, LLC (PPD) (US_7840419, US_7647235, US_7983936, US_8145504, US_8145505); and patent application for a combination of Ketamine plus Scopolamine in Major Depressive Disorder (MDD), licensed by MGH to Biohaven. Patents for pharmacogenomics of Depression Treatment with Folate (US_9546401, US_9540691). Copyright for the MGH Cognitive & Physical Functioning Questionnaire (CPFQ), Sexual Functioning Inventory (SFI), Antidepressant Treatment Response Questionnaire (ATRQ), Discontinuation-Emergent Signs & Symptoms (DESS), Symptoms of Depression Questionnaire (SDQ) and SAFER; Lippincott, Williams & Wilkins; Wolkers Kluwer; World Scientific Publishing Co. Pte. Ltd. M.F. has not done any personal consulting. Any consulting he has done has been on behalf of Massachusetts General Hospital. There are no conflicts of interest with the work conducted in this study. The other authors have no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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