

# Reward Processing After Catecholamine Depletion in Unmedicated, Remitted Subjects with Major Depressive Disorder

Gregor Hasler, David A. Luckenbaugh, Joseph Snow, Noah Meyers, Tracy Waldeck, Marilla Geraci, Jonathan Roiser, Brian Knutson, Dennis S. Charney, and Wayne C. Drevets

**Background:** We investigated whether performance on a reward processing task differs between fully remitted patients with major depressive disorder (MDD) and healthy control subjects after catecholamine depletion.

**Methods:** Seventeen unmedicated subjects with remitted MDD (RMDD) and 13 healthy control subjects underwent catecholamine depletion with oral  $\alpha$ -methyl-para-tyrosine (AMPT) in a randomized, placebo-controlled, double-blind crossover study. The main outcome measure was the reaction time on the monetary incentive delay (MID) task.

**Results:** A diagnosis  $\times$  drug interaction was evident ( $p = .001$ ), which was attributable to an increase in reaction time across all incentive levels after AMPT in RMDD subjects ( $p = .001$ ) but no significant AMPT effect on reaction time in control subjects ( $p = .17$ ). There was no drug  $\times$  diagnosis interaction on control tasks involving working memory or attention. In the RMDD sample the AMPT-induced depressive symptoms correlated with AMPT-induced changes in reaction time at all incentive levels of the MID task ( $r$  values =  $.58$ – $.82$ ,  $p < .002$ ).

**Conclusions:** Under catecholamine depletion the RMDD subjects were robustly differentiated from control subjects by development of performance deficits on a reward processing task. These performance deficits correlated directly with the return of depressive symptoms after AMPT administration. The sensitivity of central reward processing systems to reductions in brain catecholamine levels thus seems to represent a trait-like marker in MDD.

**Key Words:** Anhedonia, dopamine, major depressive disorder, monetary incentive delay task, norepinephrine, reward

Impaired function in the processing of reward-related stimuli might constitute a key behavioral endophenotype in major depressive disorder (MDD) (1–6). This behavioral deficit possibly reflects the biological endophenotype of reduced mesolimbic dopaminergic function in depression (7). A tool that potentially facilitates investigations of the relationship between central dopaminergic function and impairments in reward processing in depression is the monetary incentive delay (MID) task of Knutson *et al.* (8). This task assesses appetitive and effort-related aspects of central reward processing in humans.

An instructive paradigm for investigating the relationship between catecholaminergic function and behavior has involved the mood response to catecholamine depletion (CD), achieved by oral administration of  $\alpha$ -methyl-paratyrosine (AMPT) (1,9), a competitive inhibitor of tyrosine hydroxylase (10). The AMPT challenge studies in depression have not involved neuropsychological testing that assesses core depressive features.

The main goal of the current study was to evaluate differential responses of the brain reward system to catecholamine depletion

From the Department of Psychiatry (GH), University Hospital, Zurich, Switzerland; National Institute of Mental Health (DAL, JS, NM, TW, MG, JR, WCD), Section on Neuroimaging in Mood and Anxiety Disorders, National Institutes of Health, Bethesda, Maryland; Department of Psychiatry (BK), Stanford University School of Medicine, Stanford, California; and the Departments of Psychiatry, Neuroscience and Pharmacology, and Biological Chemistry (DSC), Mount Sinai School of Medicine, New York, New York.

Address reprint requests to Gregor Hasler, M.D., Department of Psychiatry, University Hospital, Culmannstrasse 8 8091, Zurich, Switzerland; E-mail: [g.hasler@bluewin.ch](mailto:g.hasler@bluewin.ch).

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in remitted patients with MDD and healthy control subjects with the MID task (8). The specificity of catecholamine depletion effects on reward processing was assessed by measuring AMPT-induced changes in other cognitive domains with the N-back task (working memory) and the Attention Network Test (ANT) (attention).

## Methods and Materials

### Participants

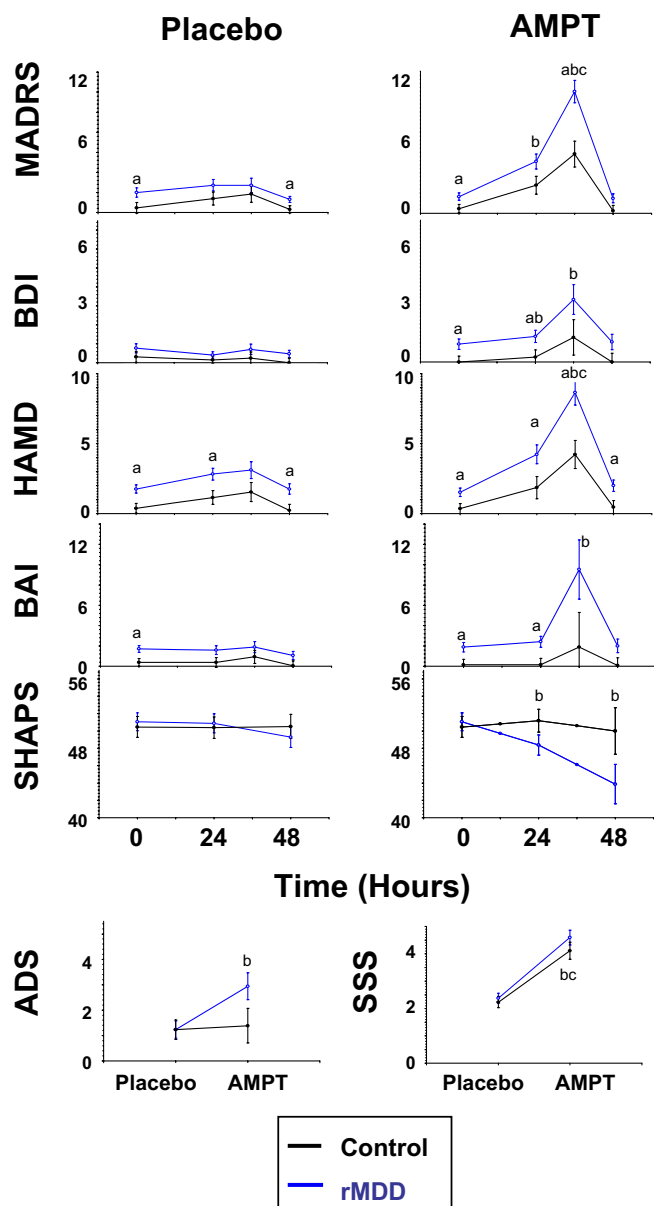
Individuals (18–56 years) either met DSM-IV criteria for MDD in full remission (RMDD) or had no history of any psychiatric disorder and no major psychiatric condition in first-degree relatives. Recruitment strategy, screening methods, and inclusion and exclusion criteria are described in (7). Written informed consent was obtained as approved by the National Institute of Mental Health Institutional Review Board. Data from the same subjects on neural responses to AMPT were published in (7).

### Experimental Design

With a randomized, double-blind, placebo-controlled crossover design, subjects underwent two identical sessions separated by at least 1 week, in which they received either a body-weight adjusted AMPT dose or placebo (as detailed in [7]). Behavioral ratings obtained are listed in Figures 1 and 2; the scoring of the educational level is described in Supplement 1.

### Neuropsychological Testing

The neuropsychological assessment started 32 hours after initiating AMPT administration and included measures of working memory (N-back task), attention (ANT), and reward processing (MID). In each session subjects were trained in each task on the day before the neuropsychological testing, and they performed a practice run immediately before testing in each session. The task order in each session was: MID, N-back, ANT. In the N-back and ANT tasks, there was no



**Figure 1.** Behavioral response to catecholamine depletion and placebo in unmedicated, remitted subjects with major depressive disorder (RMDD) and healthy subjects (control). AMPT,  $\alpha$ -methyl-para-tyrosine; MADRS, Montgomery-Asberg Depression Rating Scale; BDI, Beck Depression Inventory; HAMD, Hamilton Depression Rating Scale; BAI, Beck Anxiety Inventory; SHAPS, Snaith–Hamilton Pleasure Scale; ADS, Akathisia Determination Scale; SSS, Stanford Sleepiness Scale. a = Significant diagnosis effect (rMDD vs Controls,  $p < .05$ ); b = significant treatment effect for rMDD; c = significant treatment effect for Controls.

feedback to show that subjects performed correctly or incorrectly. The neuropsychological tests and statistical analyses are described in Supplement 1.

**Results**

Subject sample characteristics are detailed in (7). The educational level achieved did not differ significantly between groups (mean in RMDD subjects =  $6.2 \pm .95$ , and mean in control subjects =  $6.3 \pm .63$ ;  $p = .67$ ). The neuropsychological data were unavailable for between one and four RMDD subjects (depend-

ing on the task), due to technical problems with the task computer.

**Clinical Ratings**

Figure 1 shows the mean ratings of mood and anxiety symptoms, sleepiness, and akathisia for each treatment condition and group. Figure 2 shows the course of hypomanic symptoms classified by treatment and group. The statistical analyses of the clinical ratings and the neuropsychological tests are described in Supplement 1.

**N-Back Task**

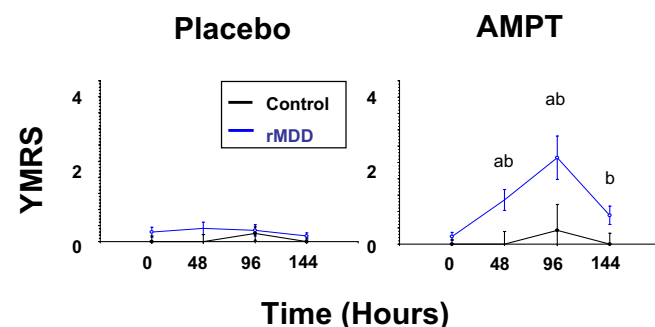
The RMDD subjects and control subjects did not differ significantly on either performance accuracy [ $F(1, 41.3) = .30$ ,  $p = .59$ ] or reaction time [ $F(1, 35.0) = .47$ ,  $p = .50$ ]. In pairwise comparisons the main effects of drug or diagnosis and the diagnosis  $\times$  drug  $\times$  difficulty level interaction did not approach significance on any of the four task-difficulty levels (for accuracy,  $p$  values  $> .19$ ; for reaction time,  $p$  values  $> .09$ ) (Figure 3).

**ANT**

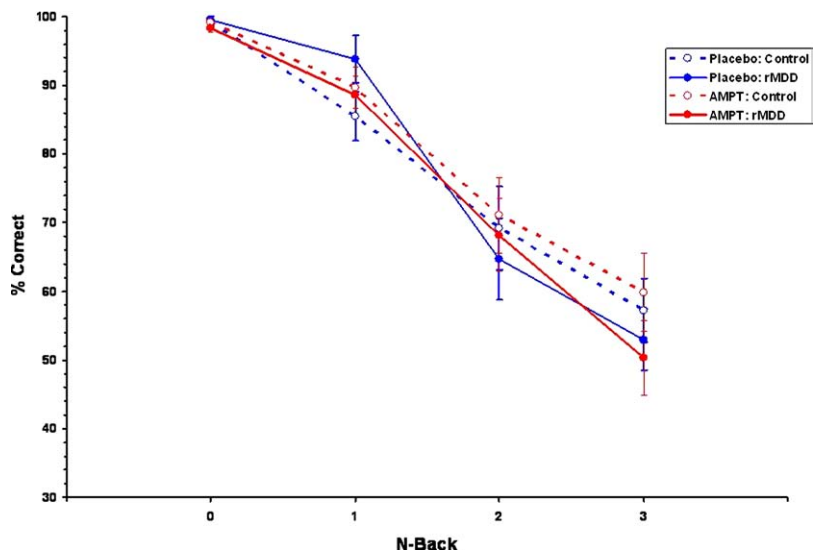
Figure 4 shows the effects of diagnosis and drug on performance, as assessed by reaction time differences on correct responses and differences in percent correct responses with respect to alertness, orientation, and executive attention. Alertness scores were lower under AMPT than under placebo, on the basis of differences in reaction time [ $F(1, 26.3) = 7.58$ ,  $p = .01$ ]. However, the drug  $\times$  diagnosis interactions involving reaction time or accuracy (% correct) did not approach significance ( $p = .53$ ). The attention orientation times (difference in reaction time between trials with and without spatial cues) were lower in RMDD subjects than in control subjects irrespective of treatment condition [ $F(1, 49.7) = 5.10$ ,  $p = .03$ ].

**MID Task**

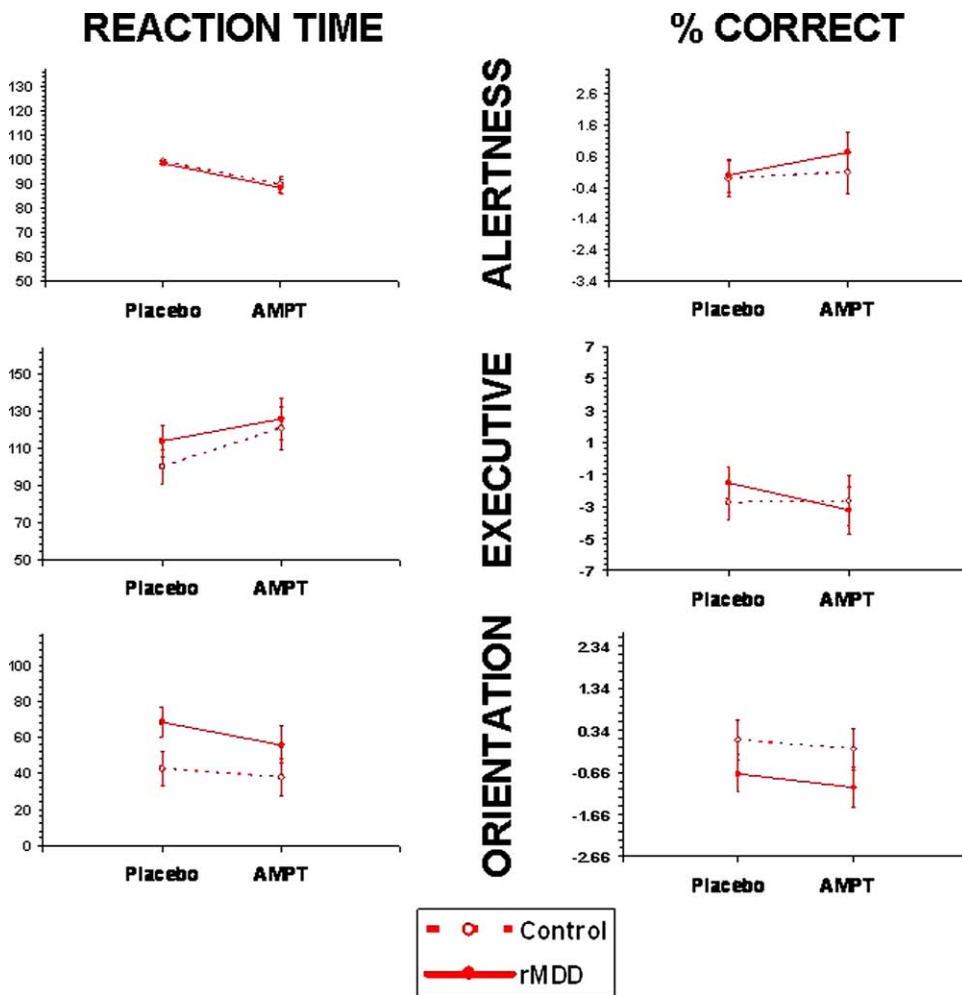
Valid MID task data from both sessions were available for 13 of the 17 RMDD subjects and all 13 control subjects. Reaction time data classified by diagnosis and drug are displayed in Figure 5. Testing within-subjects effects, we found a significant diagnosis  $\times$  drug interaction [ $F(1, 17.3) = 14.4$ ,  $p = .001$ ], which was attributable to a significant increase in reaction time across all incentive levels after AMPT in RMDD subjects ( $p = .001$ ), but no significant AMPT effect on reaction time in control subjects ( $p = .17$ ). Higher incentive levels were associated with shorter reaction times [ $F(6, 6.6) = 8.77$ ,  $p = .007$ ].



**Figure 2.** Hypomanic symptoms developing 48 hours after catecholamine depletion and placebo in unmedicated, remitted subjects with major depressive disorder (RMDD) and healthy subjects (control). AMPT,  $\alpha$ -methyl-para-tyrosine; YMRS, Young Mania Rating Scale. a = Significant diagnosis effect (rMDD vs Controls,  $p < .05$ ); b = significant treatment effect for rMDD.



**Figure 3.** Working memory performance on the N-Back task classified by diagnosis and treatment condition. The x axis indicates the difficulty level (N). AMPT,  $\alpha$ -methyl-para-tyrosine; rMDD, remitted major depressive disorder.



**Figure 4.** Reaction time and % correct responses in the attention network test classified by diagnosis and treatment condition. The y axes indicate differences between two conditions (e.g., with and without alerting cues) in terms of reaction time (msec) and the rate of correct response (%). AMPT,  $\alpha$ -methyl-para-tyrosine; rMDD, remitted major depressive disorder.

**Figure 5.** Reaction time in the monetary incentive delay task classified by incentive level, diagnosis, and treatment condition. The x axis indicates the level of incentive. Positive values refer to money that can be earned; negative values refer to money that can be lost. AMPT,  $\alpha$ -methyl-para-tyrosine; rMDD, remitted major depressive disorder.

In RMDD subjects, the AMPT-induced depressive symptoms, assessed with the intrasession change in Montgomery-Asberg depression rating scale (MADRS) scores, correlated with the AMPT-induced changes in reaction time at all incentive levels ( $r$  values ranged from .58 to .82,  $p < .002$ ) (Figure 6). Including both depressive (MADRS) and manic (Young Mania Rating Scale) symptoms in the regression analysis did not change the significance of the association between MADRS scores and MID task performance.

The RMDD subjects earned  $\$81.13 \pm 39.36$  under placebo and  $\$67.87 \pm 39.35$  under AMPT. Control subjects earned  $\$93.47 \pm 39.36$  under placebo and  $\$89.07 \pm 39.36$  under AMPT. Neither drug [ $F(1, 25.4) = .68$ ,  $p = .42$ ] nor diagnosis [ $F(1, 25.4) = 2.46$ ,  $p = .13$ ] had a significant effect on money earned, and the drug  $\times$  diagnosis interaction was not significant [ $F(1, 25.4) = .17$ ,  $p = .68$ ].

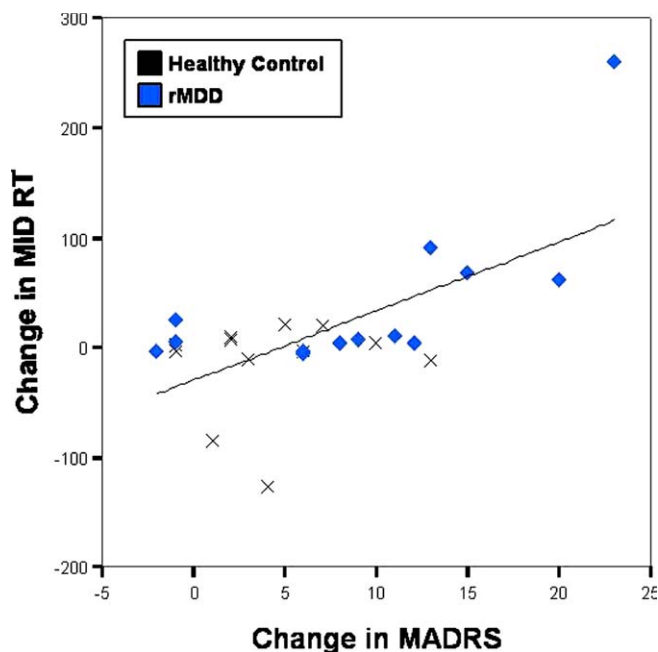
## Discussion

This study showed that RMDD subjects but not healthy control subjects show slower reaction times while performing the MID task under catecholamine depletion. Such diagnosis  $\times$  drug interactions on reaction time were not significant for the other cognitive tasks that did not involve rewarded cues, suggesting that under catecholamine depletion remitted subjects with a history of MDD manifest a relatively selective deficit on a task that involved modulation of performance by monetary reward. The correlation between AMPT-induced changes in reaction times on the MID task and AMPT-induced depressive symptoms suggest the findings hold clinical relevance.

This is the first study that examined specifically the role of catecholamines in reward processing associated with primary mood disorders. The modulation of reward-directed behavior in RMDD subjects via catecholamine depletion holds scientific

and clinical relevance given evidence that reduced dopamine neurotransmission might contribute to the anhedonia and loss of behavioral incentive in MDD (2,11,12). Moreover, dopaminergic transmission might play a role in the nonhedonic reward processing (13), because studies in experimental animals suggest that dopamine is critically involved in behavior activation, “wanting” and effortful behavior that possibly relates to depressive symptoms such as psychomotor slowing, anergia, and inertia (14). The current study extends the preclinical evidence for catecholamines’ role in reward processing (although not differentiating between the effects of dopamine and norepinephrine), by showing that catecholamine depletion reduces the ability to experience pleasure (as assessed with the Snaith–Hamilton Pleasure Scale [SHAPS]) and impairs performance on reward-directed tasks (as measured with the MID task) in susceptible individuals identified by having a history of MDD. The observation that AMPT-induced slowing in reaction time in the MID task did not significantly correlate with AMPT-induced reductions in the subjective ability to experience pleasure (SHAPS) suggests that these two measures assessed distinct aspects of the processing of rewarding stimuli.

The hypomanic rebound effect 48–96 hours after initiating AMPT most clearly differentiated RMDD subjects from control subjects. A similar rebound effect after AMPT was reported in patients with lithium-induced, long-term remission of bipolar disorder (15), but this effect was unexpected in remitted subjects with MDD. Among the three subjects whose YMRS score increased  $>7$  points, one had a first-degree relative with bipolar disorder, one had a second-degree relative with bipolar disorder, and one had a second-degree relative with a psychotic disorder (this was the only subject with a family history of psychosis).



**Figure 6.** Correlation between the AMPT-induced change in the monetary incentive delay (MID) task performance and the AMPT-induced depressive symptoms. The AMPT-induced changes in reaction time on the monetary incentive delay task (MID RT) correlated positively with the corresponding changes in depressive symptoms rated by the MADRS at 36 hours after initiating AMPT administration ( $r = .64, p = .0006$ ). The change in RT values for each subject reflects the difference in the average RT value across all incentive levels obtained under AMPT versus that obtained under placebo. The difference between the MADRS score obtained for each subject in the AMPT session versus the placebo session was calculated to reflect the magnitude of the AMPT-induced effect on depression ratings. Data from RMDD subjects are in blue; data from control subjects are in black. Other abbreviations as in Figure 1.

Several limitations of our study design merit comment. We did not include an active placebo, because the pharmacological actions of sedatives might have affected task performance. Nevertheless, it is unlikely that nonspecific sedative effects of AMPT contributed to the diagnosis  $\times$  drug interactions identified on the MID task, because the RMDD subjects and control subjects did not differ on the sedative effects of AMPT, and performance on the other neuropsychological tasks did not differ between RMDD subjects and control subjects. The relatively small sample of subjects, missing data, a mostly female sample, and the ability of RMDD subjects to remain in remission without current treatment reduced the generalizability of the results.

In summary, this study suggests that sensitivity of brain reward systems to reductions in central catecholamine levels represents a trait-like biological marker in MDD (because RMDD subjects were assessed while unmedicated and remitted). In addition, RMDD subjects were more sensitive than control subjects to developing mood changes during fluctuations in catecholamine levels. Our experiment's cross-sectional design did not allow us to determine whether the depressive response to AMPT in RMDD subjects reflected an

endophenotypic vulnerability to depression or a consequence of past illness. Nevertheless, because the AMPT-induced neuropsychological changes seem to constitute relatively specific and persistent characteristics of MDD, this study encourages further research to evaluate the neurobiological basis for differential regulation or sensitivity to changes in catecholamine levels as an endophenotype in affective illness (1,16).

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*Supplementary material cited in this article is available online.*

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