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Reduced Stress-Sensitivity or Increased Reward Experience: The Psychological Mechanism of Response to Antidepressant Medication

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Depression has often been associated with increased negative affect reactivity to stress (Stress-Sensitivity) and reduced capacity to experience pleasure or positive affect (Reward Experience). To date, no studies have prospectively examined changes in Stress-Sensitivity and Reward Experience following antidepressant treatment. The sample included 83 depressed patients and 22 healthy controls. A randomized controlled trial was carried out with patients receiving either imipramine or placebo for 6 weeks. At baseline and 6 weeks, patients and controls participated in an Experience Sampling procedure, prospectively measuring ecologically valid daily life appraisals of activities and mood states. The course of depression was assessed with the Hamilton Depression Rating Scale (HDRS). Multilevel linear regression analyses showed that patients had higher negative and lower positive appraisals of activities than controls. In addition, patients showed increased Stress-Sensitivity (negative affect reactivity to negatively appraised activities). Treatment with imipramine decreased Stress-Sensitivity and increased Reward Experience (positive affect reactivity to positively appraised activities). Changes in Stress-Sensitivity and Reward Experience were in part reducible to changes in the process of activity appraisal itself. However, increase in Reward Experience, but not decrease in Stress-Sensitivity, discriminated between patients who responded and those who did not, independent of changes in the process of activity appraisal itself. Response to treatment in depression may be conditional on restoration of hedonic capacity, the cerebral substrate of which requires further study in relation to antidepressant response. A search for (synergistic) antidepressant therapies specifically targeting ability to experience reward may be warranted.
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INTRODUCTION

Recent investigations into the factor structure of emotional experience have converged on two-factor models, often labeled positive affect (PA) and negative affect (NA) (Watson and Tellegen, 1985). Related theoretical perspectives have highlighted the functional significance of PA and NA by connecting these factors to broader affective systems governing approach and withdrawal motivation, respectively (Gray, 1973; Davidson, 1992; Depue and Collins, 1999; Watson *et al*, 1999). The PA system is associated with behavioral approach and is characterized by feelings such as enthusiasm, interest, and satisfaction. The NA system is associated with behavioral withdrawal and is characterized by feelings such as anxiety, nervousness, tension, and guilt (Watson *et al*, 1999). PA and NA reactions can thus be conceived as preparing individuals for adaptation to meaningful opportunities and threats in their environment (Watson *et al*, 1999).

In depression, emotional processing within both the NA and the PA dimension may be altered (Leppanen, 2006). First, depressed individuals and those at genetic risk for depression experience more NA (Clark *et al*, 1994) and respond with increased NA to small daily life stressors (Myin-Germeys *et al*, 2003; Wichers *et al*, 2007a, b, c). Second, anhedonia, or reduced capacity to experience pleasure or PA from events or activities that are normally rated as interesting or pleasant, is a core symptom of depression. There is experimental evidence showing lower levels of PA in depressed patients (Clark *et al*, 1994),

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decreased reward sensitivity toward positive stimuli (Sloan *et al*, 1997; Dunn *et al*, 2004; Shankman *et al*, 2007), and altered reward-related decision making (Forbes *et al*, 2007). Taken together, the findings suggest that depressed individuals show altered Stress-Sensitivity together with a diminished ability to make use of natural rewards generating positive emotions. Positive emotions, such as contentment, happiness and compassion, appear to be involved in stress resilience. They not only reduce Stress-Sensitivity in terms of altered mood response (Strand *et al*, 2006; Wichers *et al*, 2007a, b, c), but also in terms of stress-induced physical changes such as cardiovascular reactivity (Fredrickson and Levenson, 1998; Tugade and Fredrickson, 2004; Steptoe *et al*, 2007). In addition, they decrease the expression of genetic risk for depression and genetic risk for Stress-Sensitivity (Wichers *et al*, 2007a, b, c; Wichers *et al*, unpublished data). Thus, the decreased ability to generate positive emotions (decreased level of reward experience) in depressed individuals contributes to a loss of the normal protection or resilience against stress in daily life.

There has been little research on the effects of antidepressant treatment on emotional experiences in terms of alterations in Stress-Sensitivity (responding with NA to negative stimuli; hereafter: Stress-Sensitivity) and reward experience (responding with PA to pleasant stimuli; hereafter: Reward Experience). From animal studies, it is known that antidepressants reduce stress-induced brain alterations and activation of the hypothalamic-pituitary-adrenal axis, the most important brain system regulating stress responses (Connor *et al*, 2000; Basta-Kaim *et al*, 2005). In addition, antidepressant treatment in socially stressed rats restores anhedonia and motivational deficits (Von Frijtag *et al*, 2002; Rygula *et al*, 2006) and thus normalizes Reward Experience. However, there are very few studies evaluating the effects of antidepressant treatment on NA and PA reactivity in clinically depressed people. Two studies reported that both distress and anhedonia are affected by antidepressants (Tomarken *et al*, 2004; Dichter *et al*, 2005). Bhagwagar *et al* (2004) demonstrated that in individuals with a history of depression, antidepressant treatment normalized abnormal fear processing in the form of enhanced fear recognition. Other studies, sampling healthy volunteers, showed that (i) antidepressants increased the cortical response to pleasant and decreased the response to unpleasant stimuli (Kemp *et al*, 2004), (ii) antidepressant medication biased perception to positive information (Harmer *et al*, 2003, 2004), and (iii) medication decreased recognition of fearful facial stimuli (Harmer *et al*, 2004, 2006). However, healthy subjects may exhibit different responses toward the above manipulations than depressed patients (Bhagwagar *et al*, 2004). An unanswered question is whether antidepressants primarily work by normalizing alterations in Stress-Sensitivity or by increasing Reward Experience, thus enhancing the individual's emotional resilience to stress.

To date, no studies have prospectively examined changes in affective responses to negative and positive personal experiences (Stress-Sensitivity and Reward Experience, respectively) in response to antidepressant treatment. The current study investigated this issue with momentary assessment experience sampling methods (ESM), which yield data directly from the daily life of depressed patients, and thus takes into account the personal context of the individual within his or her daily life setting. Building on and extending the research reviewed above, it was hypothesized that antidepressants would alter NA responses to daily life activities appraised negatively (Stress-Sensitivity) and increase PA responses to daily life activities appraised positively (Reward Experience). In addition, it was examined to what degree changes in emotional experience in response to daily life activities coincided with clinical improvement, to elucidate the affective pathway underlying antidepressant action.

METHODS

Subjects

Eighty-three patients with a DSM-IV diagnosis of current major depressive disorder were recruited in eight primary care practices in the Netherlands (for full details concerning diagnosis and screening, see Barge-Schaapveld and Nicolson (2002)). Data were collected in the period between 1995 and 1996. Inclusion criteria were age between 18 and 65 years, a score at study entry of $\geqslant$18 on the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), and a score $\geqslant$4 on the Clinical Global Impression (Guy, 1976). Exclusion criteria included major medical disorders and current use of psychotropic medications, except for the occasional use of temazepam.

A control group of 22 healthy individuals was recruited with sociodemographic characteristics similar to those of the patient group to provide normal reference values for ESM measures (for details, see Barge-Schaapveld *et al* (1999)).

All subjects gave written informed consent. The study was approved by the standing medical ethics committee.

Study Design

The study was conducted in a primary care setting in a sample of depressed outpatients. During an initial baseline week, participants received no treatment in any form. Thereafter, patients were randomly assigned to twice daily, double blind, 6-week treatment with either a tricyclic antidepressant (TCA) (imipramine: starting dose of 50 mg/day, increased to 200 mg/day over the first week of treatment) or placebo (starting with one capsule per day, increased to four capsules over the first week of treatment). In case of intolerance, the dose could be decreased to either 100 mg/day of imipramine or two placebo capsules per day. The healthy control subjects served as reference group and were not randomized to either antidepressant or placebo treatment. All subjects participated in the experience sampling procedure at baseline and at week 6. In addition, the depressed patients underwent semi-structured interviews at regular intervals to evaluate their level of depressive symptoms.

Experience Sampling Method

Experience sampling method is a structured diary technique to assess subjects in their daily living environment, which has been validated for the use of studying the immediate

effects of stressors on mood (Csikszentmihalyi and Larson, 1987; DeVries, 1992; Delespaul, 1995; Myin-Germeys *et al*, 2003; Peeters *et al*, 2003). Subjects received a digital wristwatch and a set of ESM self-assessment forms collated in a booklet for each day. The wristwatch was programmed to emit a signal ('beep') at an unpredictable moment in each of ten 90-min time blocks between 0730 and 2230 hours, on 6 consecutive days. After each beep, subjects were asked to fill out the ESM self-assessment forms to record current thoughts, current context (activity, persons present, and location), appraisals of the current situation, and mood. All self-assessments were rated on 7-point Likert scales. Trained research nurses explained the ESM procedure to the participants during an initial briefing session. Subjects were instructed to complete their reports immediately after the beep, thus minimizing memory distortion, and to record the time at which they completed the form. To determine whether subjects completed the form on time, self-reported times were compared to the actual beep times. All reports not filled in within 15 min after the beep were excluded from the analysis, as previous study (Delespaul, 1995) has shown that reports completed after this interval are less reliable and consequently less valid. For the same reason, subjects with fewer than 20 valid reports (out of 60 maximum) were excluded from the analysis (Delespaul, 1995). ESM test-retest reliability was examined. Mean levels of PA, NA, and appraisal of activities were stable over a period of 6 weeks in the group of healthy individuals (Barge-Schaapveld, 2001).

Measurements

The 17-item HDRS was administered by the treating physician (general practitioner—GP) at screening, baseline, and week 6 to evaluate the level of depressive symptoms. All participating GPs had completed a standardized training for the HDRS procedure.

Daily life activity appraisal: stress and reward. To define stress and reward in relation to ecologically valid daily activities, ESM self-rated appraisals of ongoing activities were used, consistent with several previous studies of emotional reactivity to appraised daily activities and contexts (Myin-Germeys *et al*, 2001, 2003; Myin-Germeys and van Os, 2007). Self-report items on current activity were rated on a Likert scale (with $1 =$ not at all and $7 =$ very). Factor analysis supported inclusion of three items on activity appraisal, namely: 'do you enjoy this activity,' 'does this activity require effort,' and 'are you skilled at doing this activity.' On the basis of these ratings, a variable reflecting 'activity-related stress' and one reflecting 'activity-related reward' were created. For activity-related stress, the positive appraisals 'do you enjoy the activity' and 'are you skilled at doing this activity' were first recoded in reverse, so that higher scores represented more negative appraisals (low enjoyment and low skill, respectively). Then, low scores ($\leqslant 4$) on all three scales were set to zero and the remaining values were recoded ($5 = 1$, $6 = 2$, $7 = 3$), so that only appraisals with a negative valence contributed to the summed activity-related stress score. Similarly, to create the variable activity-related reward, the item 'does this activity require effort' was first recoded in reverse so that high scores reflected lower appraised effort, low scores ($\leqslant 4$) on this recoded item and the other two appraisal items were set to zero, and higher scores were recoded ($5 = 1$, $6 = 2$, $7 = 3$) before calculating a sum score for activity-related reward.

Mood states. At each beep, ESM mood adjectives were assessed, conform previous study (Barge-Schaapveld and Nicolson, 2002). Factor analysis, using principal component analysis with oblique rotation, was used to generate a factor representing PA and one representing NA. The mood adjectives 'cheerful,' 'content,' 'energetic,' 'calm,' 'alert,' 'enthusiastic,' 'strong,' and 'happy' loaded on the PA factor whereas 'hostile,' 'depressed,' 'tensed,' 'insecure,' 'lonely,' 'anxious,' 'guilty,' 'hurried,' and 'irritable' loaded on the NA factor. The item 'I feel tired' was left out of the constructed scales because its loading was not specific for either NA or PA.

Statistical Analyses

Experience sampling method data have a hierarchical structure. Thus, multiple observations (level 1) were clustered within subjects (level 2). Multilevel analysis takes the variability associated with each level of nesting into account (Snijders and Bosker, 1999). Multilevel linear regression analyses, using the XTREG command in STATA 9.1 (StataCorp, 2005) were applied to the data.

'Stress-Sensitivity' was conceptualized in the analyses as the effect of stressful daily life activities on NA (ie the effect of the activity-related stress score on NA). Similarly, 'Reward Experience' was conceptualized as the effect of positively appraised daily life activities on PA (ie the effect of the activity-related reward score on PA). First, it was examined whether depressed patients differed at baseline from healthy controls in terms of daily life Stress-Sensitivity and Reward Experience by assessing the two-way interaction between group status (healthy or depressed) and appraisal in the models of NA and PA, respectively. In addition, a variable was created dividing all observations of appraisals into four categories (from low to high scores) with equal number of observations (quartile groups). This variable was used to examine a possible dose-response effect of valence of appraisal on differential mood response in depressed patients *vs* healthy controls. Effect sizes of the interactions between the four levels of appraisal on the one hand and group status on the other were calculated by applying and testing the appropriate linear combinations using the STATA LINCOM command. Main effects and interactions were assessed with the Wald test (Clayton and Hill, 1993).

Second, it was examined whether antidepressant treatment with imipramine decreased Stress-Sensitivity relative to the placebo group. To effectuate this, NA was regressed on the three-way interaction 'time (6 weeks compared to baseline) $\times$ treatment group (placebo *vs* TCA) $\times$ activity-related stress appraisal.' Similarly, the effect of treatment on increase in Reward Experience was examined. Again, effect sizes of treatment group on the changes (baseline—week 6) in Stress-Sensitivity and Reward Experience were calculated by applying and testing the appropriate linear combinations using the STATA LINCOM command. Main effects and interactions were assessed with the Wald test (Clayton and

Hill, 1993). Given relatively low power, three-way interactions of $p \leqslant 0.1$ were considered sufficiently suggestive for follow-up and calculation of stratified effect sizes.

Third, patients were categorized as responders or non-responders to treatment, to determine the degree to which a decrease in Stress-Sensitivity or an increase in Reward Experience over the 6 weeks of treatment was associated with clinical improvement, stratified by treatment group (placebo or TCA). To maximize statistical power, the sample was divided according to the median split on the percentage decrease in HDRS symptom score from baseline to 6 weeks: the responder group included patients in the upper half of the HDRS distribution of change and the non-responder group those in the lower half of the HDRS distribution of change. Associations between responder status and changes in Stress-Sensitivity and Reward experience were calculated by applying and testing the appropriate linear combinations, using LINCOM; significance was assessed using the Wald test (Clayton and Hill, 1993).

RESULTS

Patient Sample

Of 83 depressed patients, 11 were excluded on the basis of the described inclusion and exclusion criteria. Reasons were use of psychotropic medication, abnormal ECG, and HDRS lower than 18; one eligible subject was excluded due to an error in the randomization procedure. Five subjects were later excluded, because they failed to complete at least 20 valid ESM reports at baseline, (see ESM, above). One depressed subject had partially missing data for PA and NA, leaving 65 depressed patients (imipramine group: 33; placebo group: 32) for the baseline analyses. For the follow-up analyses, two additional subjects were excluded who completed fewer than 20 valid ESM reports at week 6. Of the 63 remaining patients, 49 (78%) completed the first 6 weeks of treatment. Analyses concerning changes over time in Stress-Sensitivity and Reward Experience were based solely on data of subjects who completed treatment. The dropouts showed a trend toward higher PA at baseline ($B = 0.31$, $p = 0.09$) compared to the completers. There were no other significant baseline differences in mood, stress appraisal, or emotional reactivity between these two groups.

Subject Characteristics

Patients ranged in age from 25 to 59 years (mean = 42.7). The majority were women (72%) and married (68%). Most had a regular job (46%) or were housewives (25%).

Baseline average HDRS score was 23.9 (SD = 3.1; range: 19–30). At week 6, average HDRS score was 10.6 (SD = 6.5; range: 0–24). Mean HDRS scores at week 6 for the imipramine (8.5) and placebo (12.6) group differed significantly ($B = -4.14$, $p = 0.024$). For responders as defined above, mean HDRS score at week 6 was 5.2 (SD = 3.0; range: 0–9) and for non-responders 15.4 (SD = 4.6; range: 8–24). According to the common definition of remission as an HDRS score <8 (Ballesteros *et al*, 2007), none of the non-responders had thus achieved remission. The mean percentage decline in HDRS score was 55% (SD = 28.3; range: −10 to 100%). Only one subject increased in HDRS score (with 2 points) and one showed no change. For mean activity-related and mood appraisals see Table 1. Correlations between activity-related stress and reward (Table 2a) and between PA and NA (Table 2b) are depicted in Tables 2a and b. There were significant main effects of 'time' on both activity-related stress appraisal ($B = -0.15$, $p < 0.001$) and activity-related reward appraisal ($B = 0.11$, $p < 0.001$). In addition, there were suggestive or significant associations between percentage decline in HDRS scores over time and activity appraisals ($B = -0.01$, $p = 0.086$ for activity-related stress; $B = 0.02$, $p = 0.004$ for activity-related reward).

There were no large or significant initial differences between the two treatment groups with respect to socio-demographic characteristics, HDRS ratings, or activity appraisal. Patients randomized to the TCA group did not differ significantly at baseline in Reward Experience (ie effect of activity-related reward on PA) from the placebo group ($B = -0.009$, $p = 0.17$). Similarly, there was no baseline difference in Stress-Sensitivity (ie the effect of the activity-related stress score on NA) ($B = 0.005$, $p = 0.7$). At week 6, patients in the TCA group complained more frequently about having 'a dry mouth' ($B = 0.9$, $p = 0.032$) than those in the placebo group, whereas 'headache,' 'dizziness,' 'nausea,' 'drowsiness,' and 'other complaints' were reported equally or less often in the imipramine group compared to placebo. As control subjects were frequency matched for demographic characteristics, there were no differences between patients and healthy controls in mean age, sex distribution, living situation (alone or not), or work

Table 1 Means (Standard Deviation) for Activity-Related Stress and Reward Appraisal, NA, PA

				Patients (week 6)		Patients (week 6)	
	Controls (baseline) no treatment[a]	Patients (baseline)	Controls (week 6) no treatment[a]	TCA	Placebo	Responder	Non-responder
Activity-related stress appraisal	0.39 (0.3)	1.52 (1.1)	0.66 (1.3)	1.11 (0.9)	1.41 (1.5)	0.74 (0.7)	1.73 (1.4)
Activity-related reward appraisal	5.44 (1.5)	3.22 (1.5)	5.00 (1.3)	3.52 (1.9)	3.39 (1.6)	4.20 (1.6)	2.80 (1.5)
Negative affect	−0.66 (0.1)	0.47 (1.0)	−0.67 (0.2)	0.25 (0.8)	0.71 (1.1)	−0.42 (0.4)	0.36 (1.1)
Positive affect	0.94 (0.7)	−0.54 (0.6)	0.86 (0.8)	−0.28 (0.8)	−0.02 (0.7)	0.37 (0.7)	−0.58 (0.5)

Means are stratified by TCA/placebo or responder/non-responder.
[a]Controls served as a reference group only and were not randomized to treatment.

Table 2a Correlations Between Activity-Related Stress and Activity-Related Reward for all Groups at all Time Points, Corrected for Multiple Measurements Within each Subject

	Controls	Patients	
Baseline	0.52	0.58	
		Placebo	TCA
Week 6	0.40	0.67	0.60
		Non-responders	Responders
		0.60	0.55

Table 2b Correlations Between Negative and Positive Affect for all Groups at all Time Points, Corrected for Multiple Measurements Within each Subject

	Controls	Patients	
Baseline	0.02	0.26	
		Placebo	TCA
Week 6	0.10	0.46	0.46
		Non-responders	Responders
		0.27	0.09

status (see Barge-Schaapveld *et al*, 1999 for further information).

Daily Life Stress-Sensitivity and Reward Experience in Depressed Patients *Vs* Controls

At baseline, depressed patients showed significantly higher scores on activity-related stress ($B=1.07$, $p<0.001$) and lower scores on activity-related reward ($B=-2.03$, $p<0.001$) compared to healthy controls. With regard to emotional reactivity to daily life activities, depressed patients displayed an increased NA response to activity-related stress (Stress-Sensitivity) compared to controls (χ^2 interaction $=5.26$; $p=0.022$; $B=0.109$ for depressed and $B=0.068$ for control subjects). The interaction effects showed a dose-response effect: the more negative the appraisal, the greater the difference in mood response between depressed and control subjects (Figure 1).

There was no significant difference in PA response to activity-related reward appraisals (Reward Experience) between depressed patients and healthy controls (χ^2 interaction $=1.01$; $p=0.3$).

Effects of TCA Treatment on Stress-Sensitivity and Reward Experience in Depressed Patients

There was a significant three-way interaction between treatment group, time, and activity-related stress appraisal in the model of NA ($\chi^2=7.2$, $B=-0.05$, $p=0.007$), indicating that Stress-Sensitivity decreased more strongly in the TCA group ($B=-0.073$, $p<0.001$) than the placebo group (-0.023, $p=0.04$) (Figure 2a). Also, a significant three-way

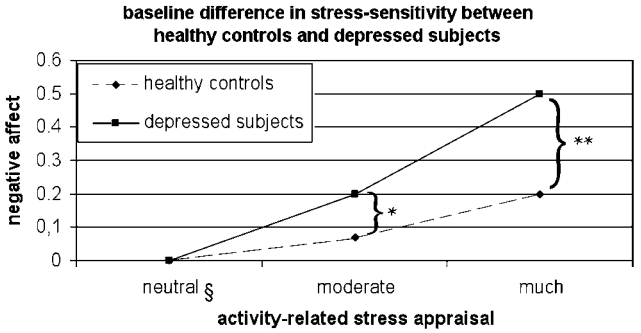

Figure 1 Difference in Stress-Sensitivity between depressed subjects and healthy controls stratified for degree of negative appraisal. *$\chi^2=4.1$, $p=0.04$. **$\chi^2=12.5$, $p<0.001$. §As the distribution of 'activity-related stress' was skewed, the first two (lowest 50% of scores) of the four categories are merged to one, representing the reference category 'neutral.'

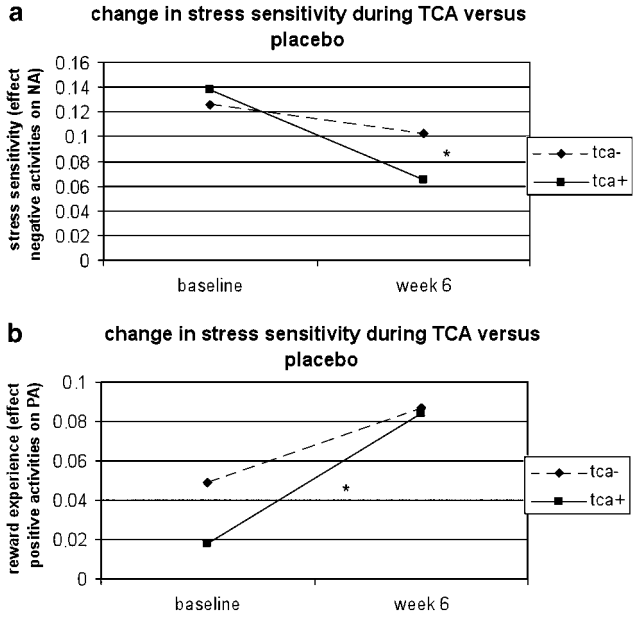

Figure 2 (a) Decrease in Stress-Sensitivity (effect of positive activities on NA) at baseline and at week 6, separated for those in the TCA and the placebo group. *$\chi^2=7.2$, $B=-0.05$, $p=0.007$. (b) Increase in Reward Experience (effect of positively appraised activities on PA) at baseline and at week 6, separated for those in the TCA and the placebo group. *$\chi^2=5.2$, $B=0.027$, $p=0.02$.

interaction between treatment, time, and positively appraised activities was found in the model of PA ($\chi^2=5.2$, $B=0.027$, $p=0.02$) (Figure 2b). Thus, Reward Experience was increased at week 6 compared to baseline, and this effect was stronger in the TCA ($B=0.066$, $p<0.001$) than the placebo group ($B=0.038$, $p<0.001$).

Both effects were independent of each other: when the first three-way interaction effect in the model of PA was controlled for change in Stress-Sensitivity, or vice versa (second interaction effect in the model of NA controlled for change in Reward Experience), interaction effects remained similar.

To investigate possible mediation by changes over the 6-week period in activity-related appraisals themselves, the analyses were repeated after adding an extra variable to

the equation, reflecting the difference in (i) activity-related stress or (ii) activity-related reward appraisal between baseline and week 6. This analysis revealed that controlling for change in activity-related appraisals reduced both interaction effects by 50%: Stress-Sensitivity ($\chi^2 = 3.0$, $B = -0.036$, $p = 0.08$) and Reward Experience ($\chi^2 = 0.93$, $B = 0.013$, $p = 0.3$).

Change in Stress-Sensitivity and Reward Experience in Relation to Treatment Response

There was no three-way interaction of responder group-time × negatively appraised activities in the model of NA ($\chi^2 = 0.27$, $B = 0.010$, $p = 0.6$). In both responders and non-responders, the NA response to activity-related stress decreased similarly after 6 weeks of active or placebo treatment (responders: $B = -0.05$, $p = 0.03$; non-responders: $B = -0.06$, $p < 0.001$) (Figure 3a). Also within the TCA group, being a responder was not associated with stronger decrease in Stress-Sensitivity, in fact, the effect was in the opposite direction (responders: $B = -0.008$, $p = 0.7$; non-responders: $B = -0.12$, $p < 0.001$). Controlling for change in activity-related stress appraisal yielded similar results.

The three-way interaction of responder group × time × positively appraised activities on PA response was statistically significant ($\chi^2 = 10.1$, $B = 0.036$, $p = 0.001$). Thus, responders ($B = 0.040$, $p < 0.001$) showed strong increases in Reward Experience from baseline to week 6, whereas non-responders did not ($B = 0.0035$, $p = 0.7$) (Figure 3b). Also within the TCA group only, the effect remained significant and was even stronger ($\chi^2 = 15.9$, $B = 0.059$, $p < 0.001$). After controlling for activity-related reward appraisal, the interactions remained significant for both the total group ($\chi^2 = 6.1$, $B = 0.032$, $p = 0.01$) and the TCA group only ($\chi^2 = 10.5$, $B = 0.054$, $p = 0.001$).

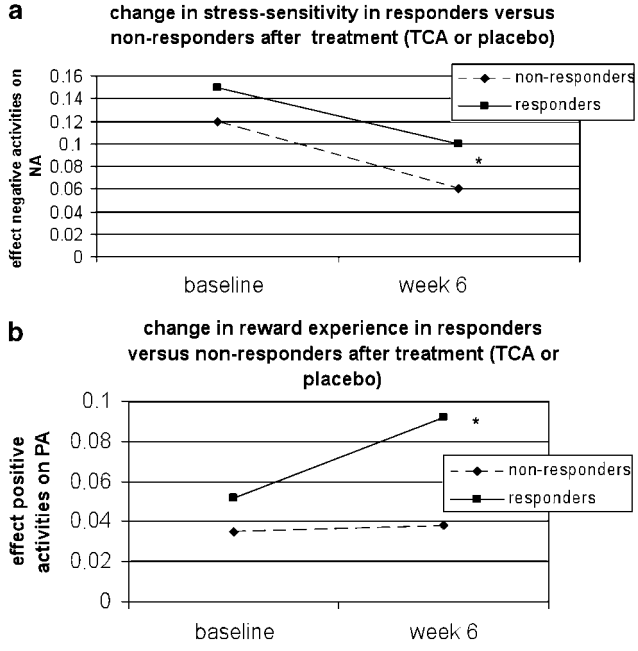

Figure 3 (a and b) Differential change in Stress-Sensitivity (a) and Reward Experience (b), respectively, for responders *vs* non-responders. a: *$\chi^2 = 0.27$, $B = 0.010$, $p = 0.6$. b: *$\chi^2 = 10.1$, $B = 0.036$, $p = 0.001$.

DISCUSSION

Findings

Depressed patients exhibited higher activity-related stress appraisals and lower activity-related reward appraisals than control subjects. However, in addition to differences in interpretation of the activity itself, the emotional reactivity differed as well. Depressed patients responded with more NA to similarly appraised activities than control subjects. Emotional reactivity associated with Reward Experience, however, did not differ between groups. In addition, antidepressant treatment with imipramine in the depressed patients decreased Stress-Sensitivity and increased Reward Experience compared to placebo treatment. These effects were brought about both by changes in emotional reactivity and by changes in appraisal of activities. Although stronger effects were found in the active treatment group, Stress-Sensitivity and Reward Experience also changed in the same direction in the placebo group. Increase in Reward Experience discriminated between treatment responders and non-responders—independently from changes in appraisal—and thus appeared to be a necessary condition for response to treatment, in contrast to changes in Stress-Sensitivity.

Emotional Processes and Biological Systems

As the two dimensions of emotional experience, NA and PA, are relatively independent, there is face validity to the hypothesis that different biological systems may be involved. There is much evidence for a role of the amygdala in stress-induced negative emotions as fear and anxiety (Vyas *et al*, 2006; Sajdyk *et al*, 2008; Yang *et al*, 2008). In addition, serotonin function has been hypothesized to regulate emotional processes related to Stress-Sensitivity (Hariri and Holmes, 2006). Animal (Lira *et al*, 2003; Wellman *et al*, 2007) and human research (Hariri *et al*, 2002; Caspi *et al*, 2003) suggest that variation in serotonin transporter (5-HTT) gene function influences depression-related behavior in response to stress and affects amygdala function. Moreover, serotonergic antidepressants seem to be more effective in treating symptoms associated with negative affectivity (fear, anxiety, and irritability) than those related to diminished PA (Nutt *et al*, 2007).

In contrast, mesolimbic brain structures are involved in mediating reward. Reduced dopaminergic activity has been associated with decreased motivation and anhedonia (Salamone *et al*, 2003; Bressan and Crippa, 2005). Dopaminergic transmission between the ventral tegmental area and the nucleus accumbens (NAc), in interaction with frontal lobe connections, mediates the affective and behavioral response to rewarding stimuli (Chau *et al*, 2004; Nestler and Carlezon, 2006). Also, equally high levels of noradrenaline and dopamine are found in the NAc (Tong *et al*, 2006), suggesting that noradrenaline is implicated in mediating reward and motivation as well. In addition, another study provided support for the supposition that noradrenergic transmission is necessary for motivated behaviors (Jasmin

et al, 2006). Imipramine has been shown in animal studies to affect both the dopaminergic (De Montis *et al*, 1990) and noradrenergic system (Linner *et al*, 1999).

Complex interactions between neurotransmitter systems take place. Dremencov *et al* (2004, 2005) showed that the increased inhibition of dopamine release in the NAc, mediated by 5-HT_{2C} receptors in rats with depressive-like behavior, is normalized by antidepressants and that restoration of the 5-HT–dopamine interaction correlated directly with improvement of behavior (Dremencov *et al*, 2004, 2005). Although it may be speculated that this interaction at the biological level reflects the interdependence between experience of stress-sensitivity and reward experience at the behavioral level, there are no data to support this hypothesis at present. Future research may address this issue. Given the current finding that reward experience mediates recovery of depression, this study supports the suggestion made by Nutt *et al* (2007) that the use of antidepressants specifically targeting reward-associated biological mediators should be explored further.

Stress-Sensitivity, Reward Experience and Depression

Interactions take place at the affective level as well. Although the two core processes of Stress-Sensitivity and Reward Experience described in this paper may fluctuate relatively independently, they may also moderate each other. For example, it has been shown that the experience of positive emotions decreases momentary Stress-Sensitivity (Wichers *et al*, 2007a, b, c). It can also be hypothesized that a decrease in emotional Stress-Sensitivity facilitates the engaging in and enjoying of activities, thus aiding in the restoration of Reward Experience (Fredrickson, 2004). In this study, patients receiving imipramine displayed strong reductions in daily life Stress-Sensitivity, albeit mediated in part by changes in appraisal. However, reduction in daily life Stress-Sensitivity was only associated with a substantial reduction in clinical symptoms (HDRS) if there was a concurrent increase in Reward Experience. An attractive speculation for further investigation is that genetic variation is involved in differential changes in Reward Experience following changes in Stress-Sensitivity. For example, recent study suggests that *catechol-O-methyltransferase* Val^{158}*Met polymorphism* genotypes, involved in the regulation of cerebral dopamine catabolism, are differentially associated with the capacity to make use of natural rewards in daily life (Wichers *et al*, 2007a, b, c). More knowledge in the field of individual genetic and biological variation in association with the above emotional processes may add to the process of prediction and improvement of treatment response to antidepressant medication.

Methodological Issues

Imipramine has a somewhat stronger impact on noradrenergic than serotonergic activity and also enhances dopaminergic activity. This represents a contrast with other antidepressant medication such as selective serotonin reuptake inhibitors. Therefore, the current results may not be generalizable to antidepressant drugs that selectively target other neurotransmitter systems.

The complaint of having a dry mouth was more often reported in the TCA group than the placebo group. *Post hoc* analyses showed that this complaint was associated with increased Stress-Sensitivity, but not with change in Reward Experience. Thus, this suggests that in reality effect sizes of treatment on decrease in stress-sensitivity might have been even larger than those reported in the study.

Although the baseline difference between groups in Reward Experience was not statistically significant, the TCA group had slightly lower initial Reward Experience than the placebo group. This meant that, although Reward Experience increased more in the TCA group, scores on this measure at 6 weeks were similar to those in the placebo group. Theoretically, it may be hypothesized that imipramine treatment would have resulted in a different effect size if baseline values had been equal. This is unlikely, however, as the effect of being a responder (for which no baseline difference in Reward Experience existed) on increase in Reward Experience was even more apparent in the TCA-only analyses than in those combining TCA and placebo (see Figure 3b). Nevertheless, replication of antidepressant treatment effects on Reward Experience is needed.

There was a suggestive baseline difference in PA between those who dropped out and those who completed the study. In addition, dropout was higher in the treatment than the placebo group. Thus, influence of differential dropout on the data may explain the low mean PA score of subjects in the TCA group at week 6 (Table 1).

It has been suggested that the ESM procedure is vulnerable to effects of poor participant compliance with the timing of self-reports (Kudielka *et al*, 2003; Broderick *et al*, 2004). In particular, fixed time sampling protocols may be problematic and can bias results. However, this study did not have a fixed time sampling frame, and the ESM procedure we used has been validated with electronic monitoring data in a different study; there, over 90% of the samples were accurately timed, and inclusion of the inaccurately timed samples did not distort the results (Jacobs *et al*, 2005).

Future Research

These findings indicate that imipramine treatment, relative to placebo treatment, decreases Stress-Sensitivity and also increases Reward Experience, although to a lesser extent. However, as an increase in daily life Reward Experience, but not a decrease in Stress-Sensitivity, was associated with treatment response, it may be beneficial to search for therapies that specifically aim at increasing the ability to experience reward (Nutt *et al*, 2006). In addition, individual factors, genetic variation, or environmental factors that impact on this ability should become the target of future investigation, so as to improve prediction of treatment response.

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