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Low-dose tryptophan depletion.

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summary of the two studies) does not mean that they were not carefully applied. When such controls are introduced, the objection concerning the posttest questionnaire loses weight. This conclusion is clearly substantiated by the bulk of studies using different masking procedures (dichotic listening, semantic priming, backward masking, binocular rivalry, etc.), all reporting evidence of nonconscious stimulus processing.

The second objection refers to the startle data themselves. It seems surprising to Drs. Grillon and Cornwell that in study 1, with only two trials, the second trial would not show the expected habituation effect, raising concerns to researchers who routinely use this technique. Therefore, the finding that the startle response increased in the second trial, when participants were shown the flower first and the spider second, is considered evidence of a serious flaw in the method. The same argument is applied to the first block of study 2. However, this argument, as we explain below, rather than weakening, strengthens the interpretation of the data as supporting the hypothesis of nonconscious processing of the fearful stimulus. Our study 1 and the first block of study 2 examine eyeblink startle in the context of simultaneously examining cardiac defense. For this reason, as reported in the paper, the intense acoustic stimulus had a duration of 500 msec (instead of 50 msec) and an intertrial interval of 120 sec. These are requirements well known to researchers familiar with the cardiac defense methodology. Cardiac defense is a robust phenomenon consistently reported in the literature since Bond's (1943) first description of the heart rate response to 'intense startling stimulation' in cats and dogs (see Turpin 1986; Vila *et al.* 1992). The response consists of a short latency acceleration (peak around 3 sec), followed by a deceleration, and then a long latency acceleration (peak between 30 and 40 sec), finishing with a second deceleration. This response pattern habituates rapidly, almost disappearing after the first stimulus presentation. For this reason, defense trials do not require a long series of trials. But the same acoustic stimulus also produces a very robust eyeblink startle response (when the stimulus has an instantaneous rise time) which, far from habituating, shows either no habituation, in the first few trials, or a clear sensitization effect in the second trial (see Ramírez *et al.* 2005; Mata *et al.* 2003). This sensitization effect is not exclusive of defensive acoustic stimuli (500 msec). Researchers familiar with the typical startle methodology (50 msec) have also reported sensitization effects in the first few trials, assuming that no practice trials are applied (see Bradley *et al.* 1996). Drs. Grillon and Cornwell have also reported sensitization effects under some emotional conditions. Therefore, our startle data should not be puzzling, even for researchers who routinely use the typical startle methodology. A potentiated startle when the spider is shown in the second defense trial and no difference when the spider is shown in the first defense trial is the correct confirmation of the hypothesis. Finally, the results of study 1 concerning cardiac defense (Ruiz-Padial *et al.* 2005) also strengthen this argument. In this case, consistent with the fast habituation of the response, evidence of nonconscious processing of the fearful stimulus comes from the potentiated cardiac response when the spider was shown in the first trial, no differences being detected when the spider was shown in the second trial, just the opposite of the startle data, as expected.

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Low-Dose Tryptophan Depletion

To the Editor:

Acute tryptophan depletion (ATD) is a popular method to investigate the effects of lowered serotonin function in humans. Acute tryptophan depletion induces a temporary depressive 'relapse' in 50–60% of remitted depressed patients treated with serotonergic antidepressants. In healthy individuals, ATD has no or minor mood effects, but cognitive effects have been found in both healthy and recovered depressed individuals (Booij *et al.* 2003).

The magnitude of the reduction of plasma tryptophan concentrations following ATD depends on the amount and composition of the amino acid mixture (Young *et al.* 1989) and whether a pre-test low tryptophan diet is included. It has been suggested that a threshold exists that needs to be exceeded before any behavioral effects occur, since studies in which the plasma tryptophan reduction was lower than 70% generally do not find any symptomatic effects (van der Does 2001b). However, depression-congruent effects on sleep architecture have been observed at moderate tryptophan reductions (Bhatti *et al.* 1998). The placebo procedure developed by Krahn *et al.* (1996) may be suitable as a low-dose ATD procedure (van der Does 2001a). Since this procedure reduces plasma tryptophan concentrations by 40–50%, and has been found not to affect mood (Booij *et al.* 2005), it allows for the investigation of possible dose-response effects.

Booij *et al.* (2005), using the Krahn *et al.* (1996) method as low-dose ATD, found that ATD had a dose-dependent effect on selective attention (Stroop color-word interference) in remitted depressed patients, but no other cognitive effects of low-dose ATD were observed. Merens *et al.* (unpublished data) observed no effects of low-dose ATD on attention, memory, and accuracy of emotion recognition in remitted depressed patients. Two recent papers have reported much stronger effects of low-dose ATD. Hayward *et al.* (2005) found that low-dose ATD had no effects on mood ratings in unmedicated recovered depressed subjects, but that it increased the emotion-potentiated startle reflex, impaired recognition of happy faces and initial recall memory and increased emotional Stroop interference. Some cognitive effects were also observed in healthy controls. Munafò *et al.* (2006) reported that low-dose ATD slightly increased self-rated depressive symptoms in medicated recovered de-

pressed patients and also increased Stroop interference for social threat words.

The low-dose mixture used by Hayward *et al.* (2005) and Munafo *et al.* (2006) consisted of eight amino-acids (31.2 g), whereas the Krahn *et al.* (1996) procedure consists of 15 amino-acids (25.7 g). We calculated the plasma tryptophan reductions obtained by Hayward *et al.* (2005), and found that low-dose ATD decreased plasma tryptophan levels by 73.9% in recovered depressed patients. The tryptophan/large neutral amino acids (LNAA) ratio decreased by 86.9%. This suggests that Hayward *et al.* (2005) studied high-dose ATD rather than low-dose. The reductions cannot be calculated from the report by Munafo *et al.* (2006), but this study used the same procedure and partly the same sample. Viewing these studies as high-dose ATD studies resolves the inconsistencies with the studies by Booij *et al.* (2005) and Merens *et al.* (unpublished data). It also explains the symptomatic effects in the Munafo *et al.* study. However, high-dose ATD would be expected to have increased symptoms in Hayward *et al.*'s paper. This may be explained by the fact that patients in this study had a relatively low number of previous episodes, which predicts a weaker response to ATD (Booij *et al.* 2002).

There is no generally accepted definition of high-dose or low-dose ATD. Hayward *et al.* (2005) presented their study as a low-dose ATD study on the basis of the amount of amino acids used. However, peripheral biochemical measures indicate that this study may be considered a high-dose ATD study. In our view, the term low-dose should reflect the decrease of plasma tryptophan concentrations and not the amount and content of the ATD mixture. Future research should carefully consider which terminology is used to prevent misinterpretation and biochemical data should be reported in detail.

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Reply to Low-Dose Tryptophan Depletion

To the Editor:

We agree with Merens and van der Does that the effect of acute tryptophan depletion (ATD) on brain serotonin function is likely to be dose-related and this in turn must depend in part on the extent to which plasma tryptophan (TRP) is lowered during the procedure. The aim of our study was to find a dose of amino-acid mixture that did not cause depressive relapse in recovered depressed patients so that we could study the effect of lowered serotonin activity on emotional processing in the absence of depressive symptomatology (Hayward *et al.* 2005). In this respect, our design was successful, and therefore the similarities between our study and that of Booij *et al.* (2005) seem to us to be more important than the differences. The report by Merens *et al.* (unpublished data) has yet to be fully published, so we are not able to comment on how far the design of the latter study informs the findings of Hayward *et al.* (2005).

Merens and van der Does suggest that the degree of TRP depletion in plasma might be a better way of distinguishing high- and low-dose ATD procedures. However, individual variation in degree of plasma TRP depletion can be substantial, and differences in apparent TRP depletion will depend on the time at which plasma TRP is sampled after depletion (5 hours in Hayward *et al.* [2005] and 6 hours in Booij *et al.* [2005]). Furthermore, the timing of the plasma TRP nadir can itself be influenced by dose (Krahn *et al.* 1996). The difference in dose of amino-acid mixture of the “low-dose” drink of Hayward *et al.* (2005) and the standard ATD mixture is 50–70 g, whereas the difference in dose between that of Hayward *et al.* (2005) and the “low-dose” drink of Booij *et al.* (2005) is < 6 g. We doubt that the small difference in dose between the latter two drinks will produce sufficiently reliable differences in biochemical and behavioral effects to merit one mixture being called “low-dose” and the other not. We therefore respectfully suggest that the term “low-dose” be retained to describe an ATD procedure that uses a dose of amino acids substantially less than that of the conventional mixture (80–100 g).

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