or by treatments for depression, is because such stimuli activate neuronal molecular signalling pathways. These pathways overlap with each other and with the signalling pathways that lead to dendritic structural changes.

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Authors' reply: It was kind of Drs S. H. & R. Zaman to take an interest in our paper. In their thoughtful response they draw attention to the time course of LTP induction (seconds to minutes), and point out that this does not correlate with the time required for the effects (presumably, clinical response) of antidepressant treatments. The key issue is not the speed with which LTP induction itself occurs, which is unchanged by stress or antidepressant treatments (Stewart & Reid, 1993). It is rather the time course of changes induced in the regulation of LTP by antidepressant treatments (the so-called 'metaplasticity' referred to in our paper) that is important. This develops gradually, requiring at least six spaced ECT treatments for maximum effect (Stewart *et al*, 1994) or 14 days of fluoxetine treatment (Stewart & Reid, 2000). Interestingly, the effects of ECT on the degree to which LTP can be induced are detectable even 40 days after the end of a course (Stewart & Reid, 2000). These periods each correlate very nicely with antidepressant response, with the last described also mirroring the time course of relapse after successful ECT treatment in humans without antidepressant prophylaxis. Changes in excitatory post-synaptic potentials are seen, however, immediately after a single electroconvulsive application in experimental studies (Stewart *et al*, 1994), but they are smaller and more transient than those seen after a series of applications. This also accords with clinical observation: severely ill patients receiving ECT often show clear but transient responses after the first treatment in a course.

Of course, these are electrophysiological observations, and they may be mediated by ultrastructural neuronal changes. In this sense, we agree with the subtle point being made by Zaman & Zaman. Our aims are to draw together rather than disaggregate structural and functional phenomena. That is why we used the term connectivity in the review to refer to both functional and ultrastructural (e.g. dendritic) changes underlying the plasticity of neuronal connections, which we wished to distinguish from more gross effects such as cell death or proliferation. The fact that "molecular signalling pathways" to "dendritic structural changes" and to LTP overlap is precisely why we classed them together as candidate contributors to the neurobiology of depressive disorder. They may be dissociable, as Zaman & Zaman point out, but this is not in itself evidence for or against the role of the regulation of LTP in affective disorder.

In any event the functional (electrophysiological plasticity) and structural changes (microanatomical plasticity) described in our review are each associated in reciprocal fashion with stress and antidepressant treatments, respectively – neither structural nor functional changes have been shown to have a causal role in depressive disorder. It does not allow that either phenomenon is a prerequisite for depressive states.

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Leptin and antipsychotic drugs

There is growing interest in the role of leptin in excessive body weight gain during antipsychotic drug treatment. Herrán *et al*'s (2001) paper is an important contribution to the field. Among other interesting findings they demonstrated that the functioning of the leptin system is preserved during antipsychotic drug administration. However, it is not "the first study analysing the effects of chronic antipsychotic medication on serum leptin levels", since other authors have published relevant data for humans and rats (Baptista *et al*, 2000; Lacruz *et al*, 2000; Melkerson *et al*, 2000).

An important finding by Herrán *et al* was that olanzapine- and risperidone-treated patients displayed the highest and lowest leptin levels, respectively, "even after controlling for BMI". This may support the contention that olanzapine is promoting a deleterious metabolic profile. That finding also prompts speculation that other mechanisms besides body weight gain could be involved in leptin elevation during antipsychotic treatment.

We have proposed elsewhere that insulin may be one of these additional mechanisms. Insulin is a powerful stimulus for leptin synthesis and secretion. Female rats with sulpiride-induced obesity unexpectedly displayed normal serum leptin (and insulin) levels (Lacruz *et al*, 2000). In addition, serum leptin and insulin levels correlated positively in healthy people and antipsychotic-treated patients (Baptista *et al*, 2000, 2001). As olanzapine strongly stimulates appetite, it may promote insulin (and leptin) secretion, with relative independence from body weight gain. Surprisingly, Herrán *et al* reported that treatment with clozapine (another agent with strong appetite-stimulating properties) was associated with leptin levels similar to those found in haloperidol- and phenothiazine-treated patients (in spite of a higher body weight gain). If it were possible for Herrán *et al* to furnish the information, readers would benefit from knowing (a) the insulin levels in these patients; (b) a comparison of leptin levels between clozapine-, olanzapine- and risperidone-treated patients and their specific matched controls; and (c) the gender distribution in these treatment groups. If olanzapine- and risperidone-treated subjects display higher and lower leptin levels, respectively, than their controls, and if the gender distribution is similar in the three treatment groups, an additional important contribution will have been brought to the field of psychopharmacology.

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