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Reply to Nathan *et al*

Reply: Indicators of Central Serotonergic Activity: How 'Specific' is Neurotransmission?

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Sir

We agree with Nathan *et al* that the association of serotonin activity and LD has not been shown in humans directly, that is, by pharmacological trials. Therefore, the observed reduction of the LD in response to selective serotonin reuptake inhibitors (SSRI) in humans mentioned by Nathan *et al* is interesting and compatible with several lines of indirect evidence published previously (Gallinat *et al*, 2005; Hegerl *et al*, 1998). However, as we stated in our recent paper and also in other reports (Senkowski *et al*, 2003), the LD is not specifically depending on serotonin system activity. Some evidence for an association of the dopamine system with the intensity dependence (but measured with visual evoked potentials) (von Knorring and Perris 1981) and the LD (shown for men only) (Bruneau *et al*, 1986) have been published. Further evidence for an association of the LD with dopamine (and serotonin) stems from a SPECT investigation (Pogarell *et al*, 2004). However, the probability of a direct dopamine modulation of the LD seems to be low because of the low dopaminergic innervation of sensory cortices (Berger *et al*, 1988), which are the main generators of the LD. It seems more likely that an interaction of dopamine and serotonin system plays a role. For instance, microdialysis investigations reported an increase of extracellular serotonin in the dorsal raphe nucleus after local infusion of selective and nonselective dopamine D2 receptor agonists (Martin-Ruiz *et al*, 2001; Ferre and Artigas 1993). Also, a recent SPECT investigation in humans indicate that SSRI modulate the central dopaminergic tone quite strongly (Pogarell *et al*, 2005). Interestingly, in the animal investigation of Juckel *et al* (1997), dopaminergic agents showed a delayed effect on the LD compared to serotonergic agents. This may indicate an indirect association of the dopamine system and a more direct relationship of the serotonin function with the LD. Similar considerations can be carried out for the results concerning the cholinergic system (Juckel *et al*, 1997) questioning the specificity of indicators of one transmitter system. Comparable to heterogeneous influences on LD, BDNF also has been shown to be not exclusively modulated by serotonin (Radka *et al*, 1996) but interacts also with dopaminergic, glutamatergic, or cholinergic neurons. In fact, short-term D2 receptor blockade reduces levels of BDNF, and BDNF is implicated in the release of dopamine and in dopamine-related behaviors induced by methamphetamine (Meredith *et al*, 2004; Narita *et al*, 2003). Concludingly, we agree with Nathan and co-workers that the specificity of LD for serotonergic function should be viewed with a certain caution, but this caution should be extended to other serotonin indicators as well.

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