frontiers in
BEHAVIORAL NEUROSCIENCE

GENERAL COMMENTARY
published: 31 October 2011
doi: 10.3389/fnbeh.2011.00074

Does reconsolidation occur in humans: a reply

Alain Brunet[1]*, Andrea R. Ashbaugh[1], Daniel Saumier[1], Marina Nelson[1], Roger K. Pitman[2], Jacques Tremblay[1], Pascal Roullet[3] and Philippe Birmes[4]

[1] *Douglas Mental Health University Institute, McGill University, Montreal, QC, Canada*
[2] *Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA*
[3] *University of Paul Sabatier, CRCA, France*
[4] *Université de Toulouse – UPS and CHU de Toulouse, Toulouse, France*
**Correspondence: alain.brunet@mcgill.ca*

A commentary on

Does reconsolidation occur in humans?
by Schiller, D., and Phelps, E. A. (2011). Front. Behav. Neurosci. 5:24. doi: 10.3389/fnbeh.2011.00024

Schiller and Phelps (2011) have provided a thoughtful and comprehensive review in the May issue of Frontiers in Behavioral Neurosciences entitled, "Does reconsolidation occur in humans?" This scholarly paper captures many of the challenges in translating the animal research on reconsolidation to humans. We agree with their main argument that there is little published evidence in humans that meets one important reconsolidation criterion, namely, that the memory-weakening treatment should be administered *after* the memory reactivation, so as not to influence the preceding memory retrieval process. However, it is unclear whether pre-reactivation propranolol significantly hampers memory retrieval. On the basis of this uncertainty, Schiller and Phelps go on to suggest that the memory impairing effects of pre-reactivation propranolol (e.g., Kindt et al., 2009; Brunet et al., 2011) *must* be explained by some process other than reconsolidation. Such a conclusion appears illogical, because if propranolol does not impair retrieval sufficiently to preclude reconsolidation, then blockade of memory reconsolidation remains a viable explanation for pre-reactivation propranolol's memory-weakening action. Indeed, the ultimate evidence for successful memory retrieval is measured during reactivation (e.g., freezing behavior in rodent fear conditioning, GSR in human fear conditioning, etc.). Therefore, any impairment of retrieval should be detected. Moreover, as shown recently by Debiec et al. (2011) immediate post-retrieval beta-adrenergic receptor stimulation enhances reconsolidation of fear conditioning in the amygdala. In this scenario, administration of propranolol following memory retrieval (which results in arousal and noradrenergic stimulation) may be too late to be effective.

So, a parsimonious explanation is that pre-reactivation propranolol did block reconsolidation to some extent in the above-mentioned studies.

Pre-reactivation propranolol studies (and other studies with a similar design) ought to be pursued vigorously because, irrespective of how the memory impairing effect is obtained, they offer the prospect of a novel approach to treating mental disorders that have at their core an emotional, usually traumatic, memory. Although Schiller and Phelps acknowledge some of the challenges of blocking reconsolidation using pharmacological means in humans, it is important to note the reasons for this difficulty. In animals, reconsolidation (i.e., protein synthesis) is believed to begin 3–10 min after memory reactivation (Monfils et al., 2009). Most of it appears to take place within the first 2 h (Przybyslawski et al., 1999) and to be over by the sixth hour (Duvarci and Nader, 2004). Considering that oral propranolol takes about 90 min to reach its peak bioavailability in human blood (Marino, 1987); and considering that only a fraction of this drug will eventually cross the blood–brain barrier to be available to exert the necessary effect, protocols that use post-reactivation propranolol are vulnerable to yielding negative results because not enough protein synthesis will have been blocked by the time the drug reaches its full effect in the human brain. Since conducting our proof-of-concept study in posttraumatic stress disorder (PTSD; Brunet et al., 2008), which used post-reactivation propranolol, we have opted to use pre-reactivation propranolol in an attempt to develop what we hope will be a more potent therapeutic protocol (see Brunet et al., 2011). It is unfortunate that this type of protocol does not meet an important scientific criterion for studies that use it to be labeled as genuine "reconsolidation" studies, but this is the price to pay for conducting sound translational research in patients. Schiller et al. (2010) are to be commended for their efforts to devise a human protocol that circumvents the problems associated with pharmacological blockade of reconsolidation by incorporating new material into a destabilized old memory, rather than simply blocking its reconsolidation. However, they have yet to show that such an approach is sufficiently potent to help patients overcome their psychological symptoms stemming from a traumatic emotional memory.

AUTHOR NOTES

Alain Brunet acknowledges receiving a salary award from the Fonds de recherche en santé du Québec (FRSQ) while working on this manuscript. Andrea Ashbaugh received a post-doctoral fellowship from the Canadian Institutes of Health Research (CIHR) while working on this manuscript. Marina Nelson holds a Tomlinson award from McGill. Requests for reprints should be sent to alain.brunet@mcgill.ca

REFERENCES

Brunet, A., Orr, S. P., Tremblay, J., Robertson, K., Nader, K., and Pitman, R. K. (2008). Effect of post-retrieval propranolol on psychophysiologic responding during subsequent script-driven traumatic imagery in post-traumatic stress disorder. *J. Psychiatr. Res.* 42, 503–506.

Brunet, A., Poundja, J., Tremblay, J., Bui, E., Thomas, E., Orr, S. P., Azzoug, A, Birmes, P., and Pitman, R. K. (2011). Trauma reactivation under the influence of propranolol decreases posttraumatic stress symptoms and disorder: 3 open-label trials. *J. Clin. Pharmacol.* 31, 547–550.

Debiec, J., Bush, D. E., and LeDoux, J. E. (2011). Noradrenergic enhancement of reconsolidation in the amygdala impairs extinction of conditioned fear in rats – a possible mechanism for the persistence of traumatic memories in PTSD. *Depress. Anxiety* 28, 186–193.

Duvarci, S., and Nader, K. (2004). Characterization of fear memory in reconsolidation. *J. Neurosci.* 24, 9269–9275.

Kindt, M., Soeter, M., and Vervliet, B. (2009). Beyond extinction: erasing fear responses and preventing the return of fear. *Nat. Neurosci.* 12, 256–258.

Marino, M. R. (1987). Pharmacokinetics and pharmacodynamics of long-acting propranolol 60-mg capsules: a comparative evaluation. *J. Clin. Pharmacol.* 27, 885–891.

Monfils, M.-H., Cowansage, K. K., Klann, E., and LeDoux, J. E. (2009). Extinction-reconsolidation boundaries: key to persistent attenuation of fear memories. *Science* 324, 951–955.

Przybyslawski, J., Roullet, P., and Sara, S. J. (1999). Attenuation of emotional and nonemotional memories after their reactivation, role of beta adrenergic receptors. *J. Neurosci.* 19, 6623–6628.

Schiller, D., Monfils, M. H., Raio, C. M., Johnson, D. C., and Ledoux, J. E., and Phelps, E. A. (2010). Preventing the return of fear in humans using reconsolidation update mechanisms. *Nature* 463, 49–53.

Schiller, D., and Phelps, E. A. (2011). Does reconsolidation occur in humans? *Front. Behav. Neurosci.* 5:24. doi: 10.3389/fnbeh.2011.00024

Received: 06 July 2011; accepted: 13 October 2011; published online: 31 October 2011.

*Citation: Brunet A, Ashbaugh AR, Saumier D, Nelson M, Pitman RK, Tremblay J, Roullet P and Birmes P (2011) Does reconsolidation occur in humans: a reply. Front. Behav. Neurosci. **5**:74. doi: 10.3389/fnbeh.2011.00074*