Brower and others have argued that the evolution of mankind might have come to a halt without optimistic illusions. With the emergence of conscious foresight (the ability to imagine one's future) came the devastating understanding that old age, sickness, decline of mental power, and oblivion await. Varki and Brower reason that this awareness on its own would have interfered with our daily function, bringing the activities needed for survival to a stop. However, if conscious foresight evolved alongside optimistic illusions, it would not have become an evolutionary psychological barrier.

Conclusion

Research on the optimism bias suggests an important divergence from classic approaches to understanding mind and behaviour. It highlights the possibility that the mind has evolved learning mechanisms to mis-predict future occurrences, as in some cases they lead to better outcomes than do unbiased beliefs.

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Department of Cognitive, Perceptual and Brain Sciences, Division of Psychology and Language Sciences, University College London, 26 Bedford Way, London WC1H 0AP, UK.
E-mail: t.sharot@ucl.ac.uk

Correspondences

The rubber hand illusion increases histamine reactivity in the real arm

N. Barnsley[1,2], J.H. McAuley[1,2], R. Mohan[1,2], A. Dey[1,2], P. Thomas[2,3], and G.L. Moseley[1,4]

Most people are convinced that their body parts are in fact their own, but in some clinical conditions, this sense of ownership can be lost [1]. Perceptual illusions, most famously the rubber hand illusion (RHI) [2], demonstrate that a sense of ownership over a body part (or an entire body [3]) that is not in fact ours can be easily induced in healthy volunteers. But does illusory ownership over an artificial body part have consequences for the real body part, the one that has been 'replaced'? Recent data show the RHI induces a small but robust drop in skin temperature of the real hand. That is, blood flow to the 'disowned' hand seems to be selectively reduced [1]. Such a finding is particularly relevant to the immune system because a primary role of the immune system is to 'discriminate self from non-self' [4]. We predicted that the innate immune system may be upregulated in a manner consistent with rejection of the replaced hand. Consistent with this prediction, we report here that the RHI increases histamine reactivity, which is a key final pathway of the innate immune response and has been implicated in autoimmune disorders, including multiple sclerosis [5]. Our finding has direct implications for autoimmune disorders and a range of neurological and psychiatric conditions characterised by a disrupted sense of ownership over one's body (see [1] for a list of conditions), and has broader implications that extend well beyond previous assertions about the mind-body link.

We undertook an initial pilot study that showed elevated histamine reactivity, measured by the size of the flare response, when the histamine was applied in conjunction with the RHI (see Supplementary Information for details). In the subsequent single-blind randomised experiment, 34 healthy naïve volunteers (21 females; mean ± SD age = 22.6 ± 2.5 years) underwent bilateral histamine applications under two different conditions. The RHI was induced in seated participants using the usual method [2]. After the illusion was established, participants closed their eyes. The skin was pricked (1 mm standardized point) at standardized locations on the volar aspect of both arms. Histamine, and antigen and saline controls, were applied to both arms. Both forearms and the rubber arm were covered with a tissue so the participant could not see the topical reactions. Participants then opened their eyes. The illusion was reestablished every three minutes by 20 seconds of synchronous stroking. For the control condition, we also stroked for 20 seconds every three minutes. The vividness of the illusion was monitored subjectively using Item 3 of the established questionnaire [2], which is known to correlate tightly with proprioceptive drift, a behavioural index of the illusion's vividness [6]. We confirmed this tight correlation in our pilot study (see Supplemental Information).

After ten minutes, the equipment was dismantled and a separate investigator, who was blinded to condition, arm and applied substance, entered the room, marked the area of induration with a felt pen, and photographed it from a standardized location 35 cm above the midpoint between the wrists of the participant. Room lighting and camera zoom were fixed. Both arms were in the one image. The size of the wheal was measured by two investigators, who were also blinded to subject, condition, arm and applied substance. Participants returned 10 ± 7 days later to perform the second condition of the experiment. The experimental arm (left or right) and the order of conditions were randomized.

Histamine always caused a wheal response, but the size of the wheal depended on the arm involved and on the experimental condition. That is, the wheal was bigger on the experimental arm during the illusion than it was on the control arm during the illusion or on either arm during the control condition (arm x condition interaction ($F(1,30) = 4.9$, $p = 0.034$; post-hoc $p < 0.05$ for all;

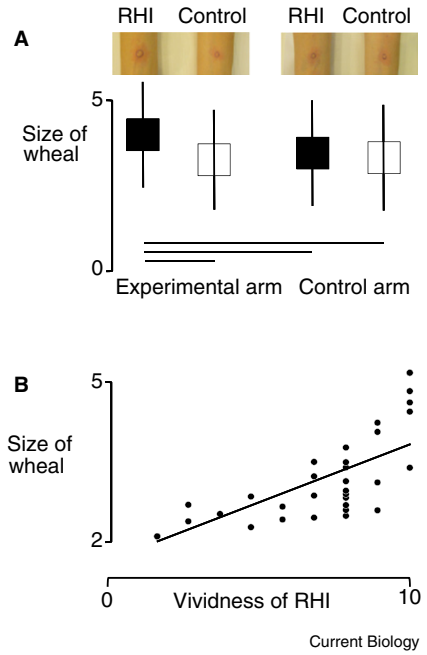

Figure 1. The size of the wheal response and its relationship to the vividness of the rubber hand illusion.
(A) Mean (squares) and standard deviation (error bars) of the surface are of the wheal in thousand pixels, for the experimental arm and control arm during the rubber hand illusion (RHI; filled squares) and the control condition (open squares). Images show each wheal from a representative participant. The reddening is the flare response. The wheal has been traced by an investigator blinded to condition and experimental arm. Horizontal lines denote difference at p = 0.05. (B) Scatterplot of the size of the wheal response on the experimental arm (vertical axis) and the vividness of the RHI (horizontal axis) for each participant in the RHI condition.

Figure 1A). For the illusion condition, the vividness of the illusion was related to the size of the wheal on the experimental arm, expressed as a proportion of the wheal on the control arm (r =0.62, p = 0.01; Figure 1B).

These results clearly show that illusory ownership over an artificial arm increases histamine reactivity in the real arm, as though the actual arm is being 'rejected'. That is, it is as though the cortical representation of the rubber arm is replacing that of the actual arm, rather than simply amalgamating with it.

Strengths of this study include a sufficiently large sample to randomize both the experimental hand and the order of conditions; blinded and cross-checked assessment of the wheal, and completely naïve participants. The effect was not dependent on stroking the arm because the arm was stroked in an identical way during both conditions, and it was not a body-wide effect, related, for example, to arousal, because only the experimental arm had an increased wheal with the RHI. That the pilot study showed a very similar effect on the flare response implicates histamine reactivity rather than modulation of a wheal-specific mechanism. Finally, that the second experiment replicated the results of the pilot study further increases confidence in the finding.

Our results are most obviously attributed to the two components of histamine reactivity — vasodilation — the reddening response, called the 'flare', which was detected in our pilot experiment (Supplemental Table S1); and plasma extravasation — the raised skin around the area, the 'wheal'. Vasodilation is mediated by H2 receptors on vascular smooth muscle and plasma extravasation is mediated by H1 receptors causing endothelial separation and increased local vascular permeability. Histamine reactivity could be elevated via decreased local metabolism of histamine or decreased antagonism of histamine by compounds that maintain vascular integrity, such as adrenaline. Another explanation worthy of exploration relates to the clinical condition of scleroderma, a chronic autoimmune disease, primarily of the skin, and a protein called endothelin. Endothelin causes both vasoconstriction and extravasation *in vitro* [7]. The skin lesions in scleroderma involve extravasation and are improved by endothelin antagonists. Finally, there is evidence that mast cells are under neuronal control, being activated by classic Pavlovian responses and Substance P [8]. That the effect is clearly unilateral might favour the neuronal explanation, but it is currently very difficult to test because antagonists for Substance P are not available for use in humans.

Our findings extend recent work that relates the limb-specific cooling induced by the RHI to a range of clinical conditions [1] and the modulatory effect of perceived limb size over swelling evoked by movement in people with pathological arm pain [9]. Finally, the current finding is consistent with the recent proposal of a cortical body matrix that integrates perceptual and homeostatic regulation of our body [10]. Further research is needed to untangle the biological mechanisms by which illusory ownership over an artificial arm disrupts physiological regulation of the intact arm, but the current data clearly extend the link between the cortical representation of body ownership and physiological regulation of the body.

Supplemental Information

Supplemental Information includes one Table, Experimental Procedures and Results, and can be found with this article online at doi: 10.1016/j.cub.2011.10.039.

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[1]Neuroscience Research Australia, Sydney, Australia. [2]The University of New South Wales, Sydney, Australia. [3]Prince of Wales Hospital, Sydney, Australia. [4]Sansom Institute for Health Research, University of South Australia, Adelaide, Australia.
E-mail:lorimer.moseley@unisa.edu.au