Ectosomes from platelets, endothelia and leukocytes are discharged directly into the blood where they can release their content rapidly or persist in the circulation for quite some time. Ectosomes discharged to the tissue intercellular space can also release their content there, remain trapped locally or diffuse some distance. Effects are triggered when ectosomes (or their released molecules) reach their targets, often in cell types distinct from the cells of origin. Released molecules activate key cell-surface molecules, such as receptors and enzymes. Intact ectosomes can either fuse with target cells (with the ensuing incorporation of their membrane in the plasma membrane and release of the segregated package to the cytosol) or be taken up by endocytosis. The fate of the latter is variable: fusion with lysosomes; release of contents in the cytosol; or discharge to the extracellular space by transcytosis (Figure 1).

What is the role of ectosomes in cell biology, physiology and pathology?
Ectosomes are specific, multi-purpose carriers that expand the borders of cells away from the plasma membrane, establishing communication networks by which specific properties and information can be shared among cells. By delivering their molecules at distance without dilution or degradation they reproduce effects otherwise induced by direct cell–cell contact, playing major roles in the integrated functioning of tissues and organs. Digestion of the intercellular matrix by metalloproteinases activated by ectosomes can induce profound changes to the cell environment. Fusion of ectosomes at the surface of target cells delivers exogenous antigens, enzymes and other proteins to discrete sites of the plasma membrane. Concomitantly, release of the segregated protein/RNA packages to target cells can alter gene expression. This might explain, among other events, the functional and phenotypic changes taking place in stem cells without transdifferentiation, sustained by genetic information transferred from tissue cells via ectosomes. Conversely, transfer of genetic information from stem cells to target cells may redirect altered functions, inducing repair of damaged tissues without replacement of parenchymal cells. The heterogeneity of ectosomes can play different, even opposing roles. Ectosomes containing cytokines, in particular interleukin 1β, are pro-inflammatory; others, however, are anti-inflammatory. Monocyte and endothelial ectosomes are often rich in tissue factor, a potent activator of the coagulation cascade, and can therefore trigger coagulation, thrombosis and also angiogenesis. Platelet ectosomes, however, contain low levels of tissue factor, and therefore work differently. Ectosomes derived from leukocytes and platelets have profound effects on innate immunity and also on the induction of adaptive immunity, reprogramming macrophages and dendritic cells toward immunosuppression.

What about ectosomes and disease?
Great interest has been raised by the increased levels of endothelial ectosomes in the blood of patients affected by acute coronary syndromes, atherosclerosis and stroke, a finding now considered for the development of new diagnostic tests. Ectosomes of specific origin are also being studied as a target of new therapies for rheumatoid arthritis and multiple sclerosis, where ectosomes are believed to promote inflammation and cell death, and for cancer, in which ectosomes play a role in invasion and metastasis. The mechanisms of the effects on cancer are multiple. In addition to the above-mentioned roles in digestion of the intercellular matrix and immunosuppression, ectosomes can induce the horizontal transfer among tumor cells of critical molecules such as proteins (e.g. P-glycoprotein (which confers multidrug resistance to the cells), glutaminase, and fibronectin), mRNAs and miRNAs. This transfer is considered to be greatly important for cancer progression.

Where can I learn more?
Cocucci, E., Racchetti, G., and Meldolesi, J. (2009). Shedding microvesicles: artefacts no more. Trends Cell Biol. *19*, 43–51.
Mause, S.F. and Weber, C. (2010). Microparticles: protagonists of a novel communication network for intracellular information exchange. Circ. Res. *107*, 1047–1057.
Muralidharan-Chiari, V., Clancy, J.W., Sedgwick, A., and D'Souza-Schorey, C. (2010). Microvesicles: mediators of extracellular communication during cancer progression. J. Cell Sci. *123*, 1603–1611.
Sadallah,S., Eken, C., and Schifferli, J.A. (2011). Ectosomes as immunomodulators. Semin. Immunopathol. *33*, 487–496.

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Primer

The optimism bias

Tali Sharot

The ability to anticipate is a hallmark of cognition. Inferences about what will occur in the future are critical to decision making, enabling us to prepare our actions so as to avoid harm and gain reward. Given the importance of these future projections, one might expect the brain to possess accurate, unbiased foresight. Humans, however, exhibit a pervasive and surprising bias: when it comes to predicting what will happen to us tomorrow, next week, or fifty years from now, we overestimate the likelihood of positive events, and underestimate the likelihood of negative events. For example, we underrate our chances of getting divorced, being in a car accident, or suffering from cancer. We also expect to live longer than objective measures would warrant, overestimate our success in the job market, and believe that our children will be especially talented. This phenomenon is known as the optimism bias, and it is one of the most consistent, prevalent, and robust biases documented in psychology and behavioral economics.

The optimism bias is defined as the difference between a person's expectation and the outcome that follows. If expectations are better than reality, the bias is optimistic; if reality is better than expected, the bias is pessimistic. The extent of the optimism bias is thus measured empirically by recording an individual's expectations before an event unfolds and contrasting those with the outcomes that transpire. This methodology reveals, for instance, that students expect to receive higher starting salaries and more job offers than they end up getting. People tend to underestimate how long a project will take to complete and how much it will cost. Most of us predict deriving greater pleasure from a vacation than we subsequently do, and we anticipate encountering more positive events in an upcoming month (such as receiving a gift or enjoying a movie) than we end up experiencing (Figure 1A). Across many different

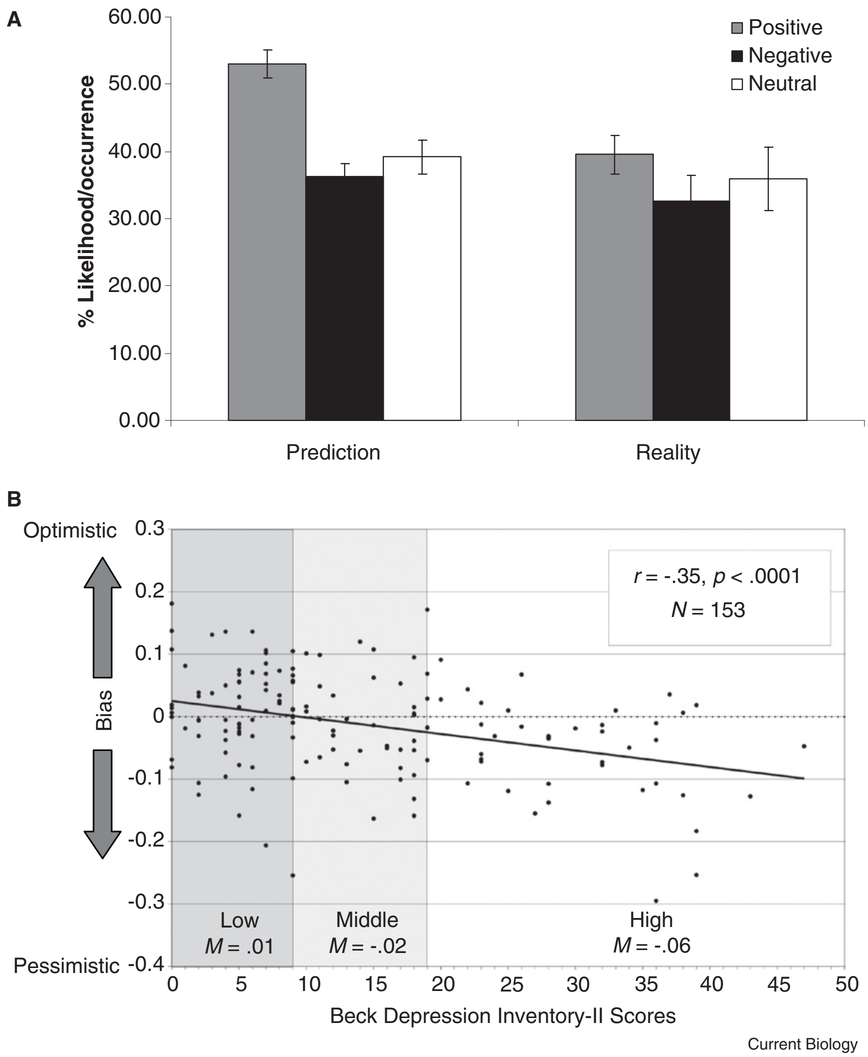

Figure 1. Optimism bias in healthy individuals and lack of optimism bias in depression.
In two studies participants were asked to predict the likelihood of different life events that might occur to them in an upcoming month (such as receiving a gift, burning dinner, getting stuck in traffic). At the end of the month they reported back which events had occurred. (A) Healthy individuals predicted positive events to be more likely than negative or neutral events. However, in reality the likelihood of positive, negative and neutral events to occur was equal (Sharot and Dudai, cited in Sharot 2011). (B) Greater pessimism bias was associated with depressive symptoms as measured by BDI-II scores (bias is measured as the difference between predicted and actual likelihood of positive events and the reverse for negative events). Individuals scoring low on depression symptoms showed an optimism bias (dark grey), individuals showing no bias in either direction were mildly depressed (light grey), and individuals exhibiting a pessimism bias scored high on depression symptoms (white). Adapted with permission from Strunk *et al*. (2006).

methods and domains, studies consistently report that a large majority of the population (about 80% according to most estimates) display an optimism bias. Optimistic errors seem to be an integral part of human nature, observed across gender, race, nationality and age.

Optimistic biases are even reported in non-human animals such as rats and birds. To study optimistic biases in birds, Matheson and colleagues (2008) taught European starlings to press a red lever whenever they heard a short (2 second) auditory tone in order to receive an immediate reward (positive outcome), and a green lever when they heard a long (10 second) auditory tone to receive a delayed reward (this is by comparison a negative outcome as birds prefer immediate reward). Colour-reward-tone associations were counterbalanced. They then tested them by presenting a medium length auditory tone. The birds were motivated to press the correct lever, because if they made a mistake they would not receive a reward at all. The results reveal that a large percentage of birds showed a bias towards pressing the lever associated with an immediate reward, suggesting that they expected a positive outcome although there was no objective reason to do so. Interestingly, birds that were kept in small cages without access to water baths and toys did not show optimistic tendencies. Their actions indicated that their expectations were unbiased rather than optimistic (in response to a medium length tone they pressed the green lever on only 50% of the trials). Comparable results have been reported in mice by Harding and colleagues (2004) using a similar paradigm, indicating that positive biases are shared by multiple other species.

There is, however, at least one group of humans who fail to show positively biased expectations — individuals suffering from depression. Strunk *et al*. (2006) have shown that while healthy humans expect the future to be slightly better than it ends up being, people with mild depression show no bias when predicting future events, and people with severe depression tend to expect things to be worse than they turn out (Figure 1B). Thus, while optimistic biases are common in the majority of humans, optimism seems to break down in major depression disorder (MDD), with pessimism being one of its key symptoms according to The Diagnostic and Statistical Manual of Mental Disorders (DSM IV).

The puzzles of unrealistic optimism

The prevalence of the optimism bias presents two puzzles. First, it is not obvious how optimism can be maintained in the face of reality. Second, it is unclear whether and why it would be adaptive to hold an optimism bias. Much recent work on optimism has addressed these two issues.

The maintenance and breakdown of optimism

Standard theories of learning hold that people adjust their expectations when faced with disconfirming information. One puzzle of optimism is thus that people maintain overly positive expectations despite a lifetime of experience with reality. There are many empirical examples of this resistance to alter optimistic expectations. For instance, highlighting previously unknown risk factors for diseases is surprisingly ineffective at altering peoples' optimistic perception of their medical vulnerability. And although people are aware that divorce rates are nearing 50% in the Western World, couples who are about to get married estimate their own likelihood of divorce as negligible. Even experts show startlingly optimistic biases; divorce lawyers underestimate the negative consequences of divorce, financial analysts expect improbably high profits, and medical doctors overestimate the effectiveness of their treatment.

Recent findings from our lab provide a mechanistic explanation of these observations. We have found that an optimism bias is maintained in the face of disconfirming evidence because people update their beliefs more in response to positive information about the future than to negative information about the future (Figure 2A). We asked participants to estimate their likelihood of encountering different aversive events in their lifetime (such as Alzheimer's disease and burglary) and then presented them with the average frequency of encountering those events. We next asked them to estimate their likelihoods once again in order to test whether they used the information provided to update their beliefs. We found that when individuals received information that was worse than their estimate (for example, when someone estimated their probability of suffering from cancer as 10% and then learned that the average probability was 30%) they did not update their estimate much the second time around. However, if a person initially provided an estimate that was more pessimistic than the information they were subsequently given (for example, estimated their own probability of suffering from cancer at 40% and then learned that the average probability was 30%), they substantially updated their estimate to more closely match the average probability. Selectively updating beliefs in response to positive information produces optimism that is resistant to change.

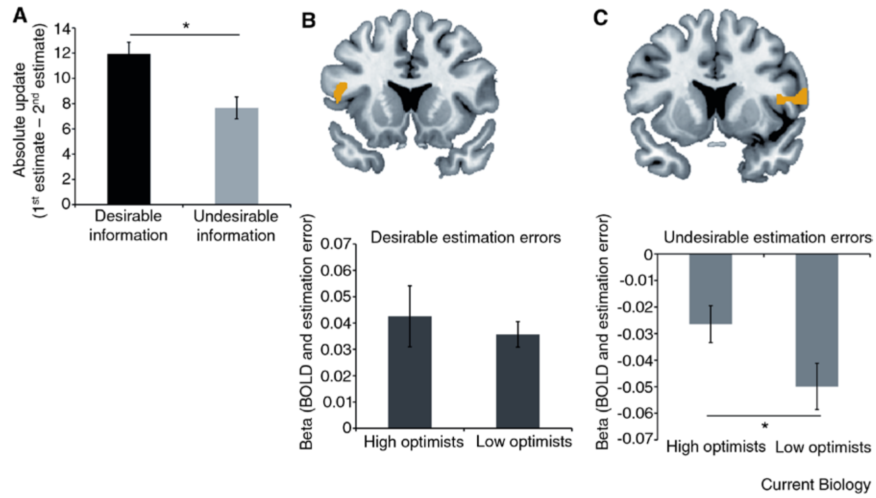

Figure 2. How optimism is maintained in the face of reality.
(A) When given desirable information about the future (such as learning that the likelihood of suffering from cancer is lower than anticipated) people updated their belief to a greater degree than when receiving undesirable information (such as learning that the likelihood of suffering from cancer is greater than anticipated). This difference was related to how well regions of the frontal lobe tracked estimation errors (that is, the differences between prior beliefs about the future and information presented). (B) Activity in the left inferior frontal gyrus was correlated with the extent of errors that resulted from positive information equally well in highly optimistic individuals and people low on optimism. (C) In the right inferior frontal gyrus activity correlated strongly with negative errors in people low on optimism, but less so in highly optimistic individuals (trait optimism is measured independently by the LOT-R scale). Adapted with permission from Sharot *et al.* (2011).

This selectivity is mediated by a failure of frontal lobe regions to code errors in prediction that would reduce positive expectations. When optimistic individuals are confronted with unexpected statistics about the likelihood of encountering negative events, their right inferior frontal gyrus exhibits reduced coding of information that calls for a negative update (Figure 2C). In particular, individuals who score high on a scale measuring trait optimism have a weaker correlation between activity in this region and the extent of negative errors in estimation. But when the information presented is better than expected, regions of the prefrontal cortex code for it efficiently both in highly optimistic and less optimistic individuals (Figure 2B). In other words, while coding for positive information about the future is intact, optimism is tied to a failure in updating from (and diminished neural coding of) undesirable information regarding the future.

Although selective updating in response to positive information is consistently observed in healthy populations, this pattern seems to be abolished, and even reversed, in people suffering from depression. It is possible that efficiently updating one's beliefs in response to negative information contributes to a pessimistic outlook that may result in the low mood characteristic of depression. The causation, however, could point in the opposite direction: low mood could cause depressed individuals to attend to negative information about the future that is congruent with their current affective state. Further work is needed to untangle these mechanisms.

An absence of optimism in depressed individuals may also relate to how future scenarios are mentally constructed. When healthy people imagine their future they tend to form positively biased scenarios, imagining positive events (such as winning a professional award) in more detail and as closer in time than negative events (such as losing a large sum of money). Mentally, people 'approach' positive future scenarios and distance themselves from negative ones. We have shown that this bias is associated with increased activation of the amygdala (involved in emotional processing) and rostral anterior cingulate (rACC, involved in emotion regulation) when people imagine positive future events relative to negative events. Furthermore, there is increased functional connectivity between the two structures when healthy individuals imagine positive scenarios relative to negative ones. We suggest that the rACC contributes to optimism by biasing attention and vigilance towards positive associations and emotions when imagining the future. Intriguingly, it is precisely these regions — the amygdala and the rACC — that show abnormal function and impaired connectivity in depressed individuals.

Further links between depression and (a lack of) optimism come from the notion that optimism relates to a person's belief in their control over future outcomes. Overestimating ones' control over events is thought to increase optimism, because people believe that if they have the ability to control future outcomes they can steer themselves in the right direction. While healthy individuals tend to overestimate the extent of control they have over events, depressed individuals do not show this tendency. Seminal work by Martin Seligman (2006) suggests that learning that one does not have control over the environment can induce depression. He has shown that when an animal is exposed to an environment in which actions do not influence outcomes, it quickly begins to show signs of depression. Seligman coined the effect "learned helplessness" and showed that, even after being transferred to an environment in which the animal can in fact determine outcomes, the animal assumes helplessness and fails to commit the actions needed to avoid negative outcomes.

Is optimism optimal?

Given that the healthy brain exhibits mechanisms that create optimistic beliefs, one can ask the teleological question of why this is. While classic theories in economics and psychology assert that correct beliefs will maximize reward and minimize loss, many sources of evidence point to the conclusion that optimism is nonetheless advantageous compared to unbiased predictions.

As discussed above, the absence of positive expectations of the future is associated with mild depression and anxiety, suggesting that optimism is vital to mental health. However, optimism is also beneficial for physical health. All else being equal, optimists live longer and are healthier. The effects can be quite substantial, with one survey of 97,000 individuals reporting that optimists are 14% less likely to die between the ages of 50 and 65, and 30% less likely to die from cardiac arrest. Optimism has also been related to extended survival time of cancer and AIDS patients.

Optimism affects physical health in at least two ways. First, expecting positive outcomes reduces stress and anxiety. This is beneficial given that chronic stress is detrimental to health, causing over-activation of the autonomic nervous system and the hypothalamic-pituitary-adrenocortical axis. Optimists have been reported to catch fewer infectious diseases and have a stronger immune system. Second, it has been suggested that optimism facilitates health-promoting actions. For example, studies show that optimistic patients are more likely to eat healthily and engage in exercise. It seems that the belief in recovery motivates the individual to act in ways that promote it.

Optimism appears to be related to success in the professional domain as well. Duke economists Puri and Robinson (2007) report that optimists work harder and longer hours, which may account for their higher pay. Indeed, optimism has been linked to achievement in education, business, sport and electoral politics. In a recent paper, Johnson and Fowler (2007) present a computational model suggesting that overestimating one's probability of success is advantageous in a world of uncertainty and competition. They suggest that if contested resources were sufficiently valuable compared to the costs of competing for them during human evolutionary history, humans would have evolved a bias to overestimate their likelihood of success.

In a recent review, McKay and Dennett (2009) conclude that optimistic illusions are the only group of misbeliefs that are adaptive. While this may indeed be the case, it is important to note that excessive optimism can also be hazardous. Underestimating risk may reduce precautionary behaviour such as safe sex, attending medical screenings or buying insurance. It could potentially promote harmful behaviours such as smoking, over-spending, and unhealthy eating due to the optimistic assumptions that unwanted future outcomes (such as lung cancer, bankruptcy and obesity) are unlikely to materialize and that positive future outcomes (such as earning larger amounts of money) are. Indeed, it has been reported that extreme optimists are more likely to smoke and less likely to save money than are mild optimists. These behaviours have traditionally been attributed to temporal discounting (overvaluing the present over the future), but studies show that when optimistic expectations are abolished, these behaviours are reduced. This suggests that choosing to engage in an act that is rewarding at present but costly in the future (smoking, unprotected sex, overeating) can be partially explained by an excess of unrealistic optimism.

The harmful influences of over-optimism likely extend to the collective behaviour of groups. For instance, the optimism bias has been named by several economists as one of the core causes of the financial downfall of 2008. Unrealistic expectation of individuals, financial analysts and government officials that the market would continue growing, despite evidence to the contrary, likely contributed to the collapse. This example may be indicative of a trend in which the negative consequences of optimism are especially pronounced in the modern world. There are two reasons why this might be. First, models of predictive bias (such as that of Johnson and Fowler) hold that the extent of unrealistic optimism should increase with uncertainty. People will show the largest bias in situations with the greatest unknowns. The modern world presents us with many such situations — whether we are dealing with unfamiliar cultures (for example, in political relations) or novel technologies (for example, internet and financial markets), modern life is rife with circumstances in which over optimism is likely to arise. Second, the modern world has increased interactions between larger numbers of individuals. Individuals' biases that are inconsequential on their own can accumulate together to produce a large bubble, such as in the case of the 2008 financial market fall.

On balance, however, it seems that the benefits of unrealistic optimism may have outweighed the downfalls. The biologists Ajit Varki (2009), Danny

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.

Further reading

Chang, E.C. (2000). Optimism & Pessimism: Implications for Theory, Research, and Practice. (American Psychological Association).
Harding, E.J., Paul, E.S., and Mendl, M. (2004). Cognitive bias and affective state. Nature *427*, 312.
Johnson, D.D.P, and Fowler, H.F. (2011). The evolution of overconfidence. Nature *477*, 317–320.
Matheson, S.M., Asher, L., and Bateson, M. (2008). Larger, enriched cages are associated with 'optimistic' response biases in captive European starlings (Sturnus vulgaris). Appl. Anim. Behav. Sci. *109*, 374–383.
McKay, R.T., and Dennett D.C. (2009). The evolution of misbelief. Behav. Brain Sci. *32*, 493–561.
Puri, M., and Robinson, D.T. (2007). Optimism and economic choice. J. Fin. Econom. *86*, 71–99.
Seligman, M.E.P. (2006). Learned Optimism (New York: Vintage Books).
Sharot, T. (2011). The Optimism Bias (New York: Pantheon Books).
Sharot, T., Korn, C.W., and Dolan, R.J. (2011). How unrealistic optimism is maintained in the face of reality. Nat. Neurosci. *14*, 1475–1479.
Strunk, D.R., Lopez, H., and DeRubeis, R.J. (2006). Depressive symptoms are associated with unrealistic negative predictions of future life events. Behav. Res. Ther. *44*, 861–882.
Taylor, S.E., and Brown, J.D. (1988). Illusion and well-being: a social psychological perspective on mental health. Psychol. Bull. *103*, 193–210.
Varki, A. (2009). Human uniqueness and the denial of death. Nature. *460*, 7256–684.
Weinstein, N.D. (1980). Unrealistic optimism about future life events. J. Pers. Soc. Psychol. *39*, 806–820.

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The rubber hand illusion increases histamine reactivity in the real arm

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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;