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The Involvement of the Orbitofrontal Cortex in the Experience of Regret

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Facing the consequence of a decision we made can trigger emotions like satisfaction, relief, or regret, which reflect our assessment of what was gained as compared to what would have been gained by making a different decision. These emotions are mediated by a cognitive process known as counterfactual thinking. By manipulating a simple gambling task, we characterized a subject's choices in terms of their anticipated and actual emotional impact. Normal subjects reported emotional responses consistent with counterfactual thinking; they chose to minimize future regret and learned from their emotional experience. Patients with orbitofrontal cortical lesions, however, did not report regret or anticipate negative consequences of their choices. The orbitofrontal cortex has a fundamental role in mediating the experience of regret.

When faced with mutually exclusive options, the choice we make is conditioned by what we hope to gain, the economist's "expected value," but it is also influenced by how we hope we will feel afterward. The emotional component of a decision may be the reason why, once we are committed to a course of action, we often prefer to ignore what would have happened if we had chosen differently (*1*), especially if the outcome turns out to be unfavorable. Missed opportunities as a result of wrong choices may indeed result in the emotion of regret (*2*). Regret is a cognitively mediated emotion triggered by our capacity to reason counterfactually. Counterfactual thinking is the mechanism by which we compare "what is" with "what might have been" (*3*, *4*). Contrary to mere disappointment, which is experienced when a negative outcome happens independently of our own decision, regret is an emotion strongly associated with a feeling of responsibility (*5*). Regret has a profound impact in decision making (*6*) and is a powerful predictor of behavior because people's choices are often made to avoid this highly unpleasant emotion (*7*, *8*).

What are the cerebral structures mediating such fundamental human emotions as regret? One potentially critical player is the orbitofrontal cortex, a structure that is connected with the dorsolateral prefrontal regions active in reasoning and planning, with limbic areas such as the amygdala important for emotion, and with other areas providing direct or indirect access to multiple sensory modalities (*9*). The orbitofrontal cortex is also active in reward evaluation and comparison (*10*–*13*). Patients with lesions in this region show poor social and individual decision-making skills and abnormal anticipatory emotional responses (*14*–*16*).

The orbitofrontal cortex thus appears to be at the interface of emotion and cognition and is ideally suited to control emotional experience through mechanisms such as counterfactual reasoning. We adopted a decision-theory framework to test the prediction that advantageous choice behavior depends on the ability to anticipate and hence minimize regret. We adapted an experimental paradigm inspired from the work of Mellers *et al*. (*5*) to analyze the emotional impact of decisions in terms of disappointment and regret and to test whether the ability to experience these emotions is mediated by the orbitofrontal cortex.

Normal subjects and patients with orbitofrontal cortex lesions were presented with a choice between two risky gambles with a monetary reward (*17*) (Fig. 1). We tested several predictions: (i) the same obtained outcome will lead to different experienced emotions depending on whether feedback about the outcome of the unchosen option is available; (ii) as compared with the emotions of normal subjects, the emotions of patients with orbitofrontal lesions will not show an effect of feedback about the outcome of the unchosen option; and (iii) choice strategy will develop as a result of the ability to take

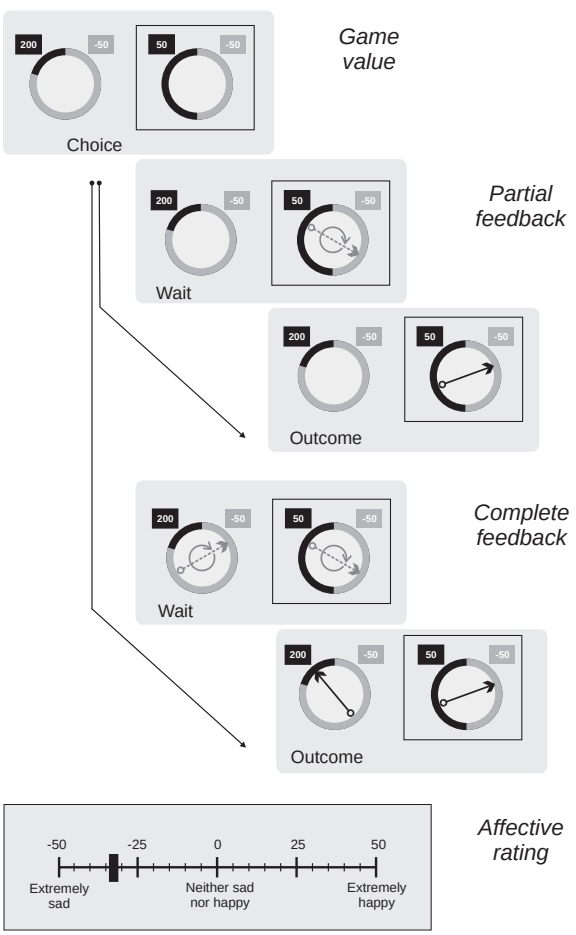

Fig. 1. Time course of a gambling trial. Two wheels appeared on a computer screen (gamble 1 and gamble 2). Each wheel had two sectors (black and light gray) associated with different value pairs. The size of each sector indicated the outcome probability. The two possible outcomes are formed by any pair of the following values: +50, –50, +200, –200 (units correspond to former French francs), associated with different outcome probabilities (0.8, 0.2, 0.5). The subject selected one of the two wheels by clicking a mouse. A rectangular box appeared around the selected wheel. In partial feedback blocks, a spinning arrow appeared only in the selected wheel, rotated for a variable duration, and stopped in one of the two sectors. Only the outcome of the selected wheel could be seen. In complete feedback blocks, a spinning arrow appeared in both the selected and the nonselected wheels. The arrows rotated and stopped, allowing the subject to view both outcomes. At the end of each trial, subjects rated their affective state using a rating scale from –50 (extremely sad) to +50 (extremely happy). SCR was also recorded.

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into account the outcome of the unchosen option in normal subjects but not in orbitofrontal patients.

The subjective emotions experienced in this gambling task depend on the values of the obtained outcome and the unobtained outcome. Other things being equal, subjects express more pleasant emotions when the obtained value is positive than when it is negative. The effect of the unobtained outcome strongly modulates that of the obtained outcome. In the partial feedback condition, disappointment is expressed in the perception of losses as more unpleasant and gains as less pleasant if the unobtained outcome from the same gamble wins 200 (units correspond to former French francs) instead of losing 200 (Fig. 2A, Wilcoxon signed-rank test, $Z = -3.703$, $P < 0.001$, for –50 obtained; $Z = -3.637$, $P < 0.001$, for +50 obtained). The emotional reaction is modulated more strongly in the complete feedback condition, showing the effect of regret. Losing 50 when the unchosen alternative wins 200 induces a strong negative feeling, whereas the same outcome is perceived as indifferent when the other gamble loses more (Fig. 2C, Wilcoxon, $Z = -3.237$, $P = 0.0012$). Even a gain of 50 can produce unhappiness if the other option wins more (Wilcoxon, $Z = -3.680$, $P < 0.001$), whereas it produces a pleasant sensation when the other gamble loses (*18*).

Direct comparisons between the two conditions show different levels of emotional involvement under complete and partial feedback. Affective ratings for a given outcome obtained in the face of a more favorable outcome of 200 for the unchosen gamble are more negative than in the face of an unobtained outcome of 200 for the chosen gamble (Wilcoxon, $P < 0.001$, for both –50 and +50 obtained outcomes). This is the signature of regret: an unpleasant emotion triggered by knowledge of the rejected alternative's outcome.

Skin conductance response (SCR) increases when learning the outcome of the gamble, revealing the emotional nature of this information. The distinction between disappointment and regret expressed by subjective affective ratings is confirmed by the physiological index of emotional reactivity, because viewing the outcome of the rejected alternative enhances SCR as compared with viewing only the outcome of the chosen gamble (Fig. 2E, paired t test, $t = -2.124$, $P = 0.0406$, two-tailed). This effect is particularly pronounced when losing as compared with winning 50, suggesting that regret potentiates more strongly an already negative emotion ($t = -2.007$, $P = 0.031$).

A very different pattern of results was observed in patients with orbitofrontal lesions. Like normal subjects, they are generally happier when winning than when losing (Wilcoxon, $Z = -3.296$, $P < 0.001$), and their SCR demonstrates clear emotional arousal when learning the outcome of the gamble. The disappointment effect, i.e., the effect of the unobtained outcome of the chosen option, is present but without as much contrast as that seen in normal subjects. When losing, patients were somewhat sadder if the unobtained outcome was a large gain than if it was a greater loss (Fig. 2B, Wilcoxon, $Z = -1.671$, $P = 0.094$, for –50 obtained). When patients won, the effect of the unobtained outcome was not significant (Wilcoxon, $Z = -1.483$, $P = 0.138$, for 50 obtained). This result suggests that they were somewhat able to think counterfactually on the chosen gamble. However, the emotions expressed by these patients are not modulated at all by the feedback on the outcome of the unchosen gamble, and they seem to experience no regret whatsoever (Fig. 2D). Sadness expressed at losing 50 is not more intense if the rejected alternative wins 200, nor is the joy felt at winning 50 tarnished by seeing that the gain would have been larger had the alternative gamble been selected [see fig. S1 for patients' individual performance and (*17*) for detailed statistical analyses]. It should be stressed that the absence of a regret effect cannot be explained by a less differentiated emotional expression or by a reluctance to use the extremes of the rating scales, because patients, like normal subjects, were shown to use the full range of the affective rating scale with the larger values of obtained outcomes (i.e., –200 and 200, fig. S2). SCR data confirm a lack of emotional reaction of the orbitofrontal patients to the outcome of the rejected gamble (Fig. 2F).

Three control patients with frontal lesions sparing the orbital area participated in the experiment. Emotional ratings show the effects of the unobtained outcome in both the partial and complete feedback condition, indicating that they responded with disappointment and regret in a manner comparable to

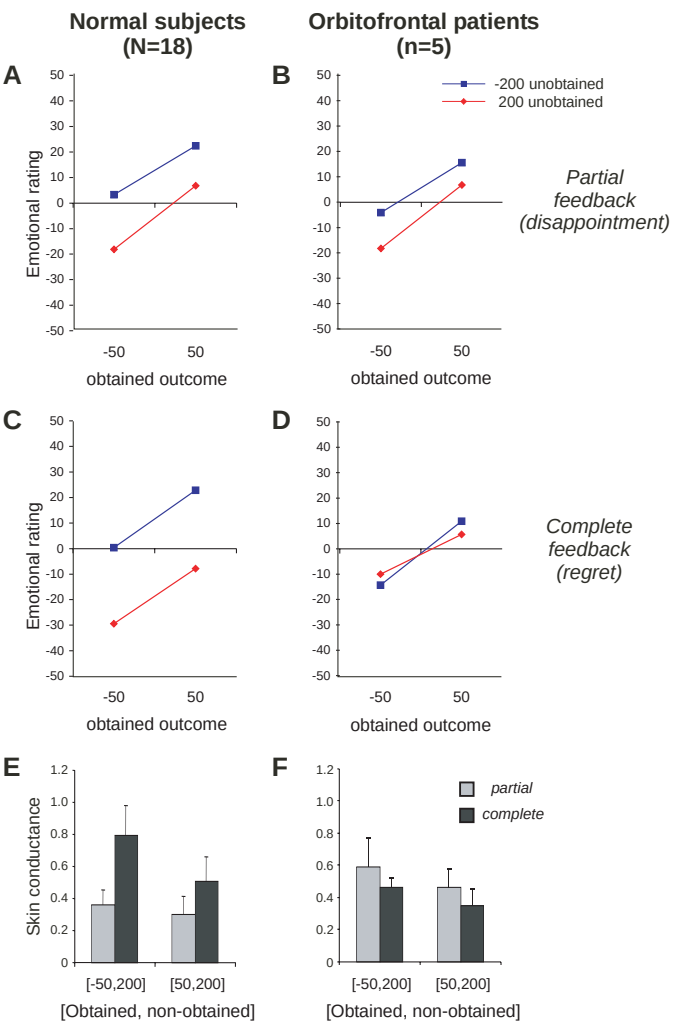

Fig. 2. Effect of the unobtained outcome of the gamble in partial and complete feedback. (**A** and **C**) Mean emotional ratings made by 18 normal control subjects for two obtained outcomes (–50 or 50) as a function of the unobtained outcome (blue line and symbols, –200; red line and symbols, 200) in the partial and complete feedback conditions, respectively. In the partial condition, the unobtained outcome corresponds to the unobtained value of the chosen gamble. In the complete condition, it corresponds to the obtained value of the nonchosen gamble. (**B** and **D**) Mean emotional ratings made by five orbitofrontal patients in the partial and complete feedback conditions, respectively. Conventions as in (A) and (C). (**E**) Mean skin conductance response (+ standard error) of normal subjects, measured at the end of arrow rotation, for the conditions in which the unobtained outcome is more advantageous than the obtained outcome (corresponding to the red curves in the graphs above). Gray bars (partial feedback) and black bars (complete feedback) are physiological markers of disappointment and regret, respectively. Regret is correlated with stronger emotional arousal. (**F**) Same data for orbitofrontal patients, showing no regret effect.

normal subjects (fig. S3), clearly showing the selectivity of the effects to the orbital region within the frontal lobe (see Fig. 3 for location of maximum lesion overlap in orbitofrontal patients). It should be stressed that the lack of regret observed in orbitofrontal patients is not due to a general lack of interest in potential monetary gains. They responded emotionally to winning and losing, as shown by the basic affective ratings. They saw the actual piles of coins building up (or down) from one trial to the next and kept track of their earnings. Neither was this indifference due to an inability to orient attention to more than one gamble at a time. Throughout the task the experimenter verified that the patients had correctly registered the outcome of each gamble before recording the affective rating.

To determine the influence of anticipated emotions of disappointment and regret on the decision process, we tested a model of choice incorporating these emotional variables as well as the expected values of the two gambles. The outcome structure of the experiment was defined so that the two gambles always differed in their expected values, but the gamble with the highest expected value won less often on average that the one with the lowest expected value. This was done to ensure that the subject would experience negative emotions on a sufficient number of trials. Under this condition, subjects could learn to choose advantageously by anticipating future emotional reactions and trying to avoid negative emotions.

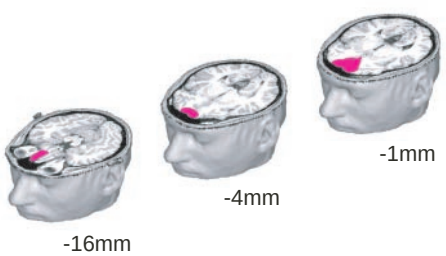

Fig. 3. Lesion overlap in the orbitofrontal cortex for the five patients. Lesion locations were reconstructed from individual magnetic resonance imaging scans. The three slice levels (in Talairach coordinates) show the region of common cortical damage, which is located in the basal and ventromedial sector of the prefrontal cortex and which includes Brodmann's areas 10, 11, 32, 24, and 47.

We tested the model exclusively with data from the complete feedback condition, considering that in the partial condition the feedback provided did not elicit regret (Table 1, regression analysis) (*17*). Patients chose only according to the expected values of the gambles (the coefficient of e is positive and significant), whereas the normal subjects anticipated regret (the coefficient of r is positive and highly significant). The results of our model show that the variable d (anticipated disappointment) is not significant for either group.

As a result of this anticipated emotional process, the normal control subjects more often chose the advantageous gamble, ending up with net gains. The mean of earnings for the normal subjects was 366.66. By contrast, the orbitofrontal patients more often chose the disadvantageous gamble, ending up with net losses (mean earnings = –110). The difference in earnings between the two groups was statistically significant (Mann-Whitney U test, $Z = 2.513$, $P = 0.0120$). The normal subjects earned significantly more in the complete condition than in the partial condition (297.22 versus 69.44, Wilcoxon, $Z = -2.902$, $P = 0.0037$), whereas there was no significant difference between patients' earnings in the partial and complete condition (Wilcoxon, $P = 1$).

In contrast to the standard theory in decision making (*19*), our results show that the emotions related to experiencing gains or losses are not independent from the alternative outcomes. Indeed, it is the counterfactual thinking between the obtained and unobtained outcomes that determines the quality and intensity of the emotional response (*20*). Regret and disappointment are elicited by two different counterfactual comparisons characterized by two different levels of personal responsibility for the consequence of one's own choices (*21*, *22*). The absence of regret in orbitofrontal patients suggests that these patients fail to grasp this concept of liability for one's own decision that colors the emotion experienced by normal subjects.

We showed that regret generates higher physiological responses and is consistently reported by normal subjects as more intense than disappointment. This was not the case in orbitofrontal patients, demonstrating that distinct neural processes generate these two emotions. The specificity of the orbitofrontal region in mediating regret is strengthened by the finding that three control patients with lesions in other parts of the frontal lobes showed normal regret levels and choice behavior in our gambling task.

Previous work implicating the orbitofrontal cortex in emotion-based decision making principally emphasized bottom-up influences of emotions on cortical decision processes (*14*, *16*). We propose a different role whereby the orbitofrontal cortex exerts a top-down modulation of emotions as a result of counterfactual thinking, after a decision has been made and its consequences can be evaluated. As shown by the model of choice, the feeling of responsibility for the negative result, i.e., regret, reinforces the decisional learning process. The orbitofrontal cortex integrates cognitive and emotional components of the entire process of decision making; its incorrect functioning determines the inability to generate specific emotions such as regret, which has a fundamental role in regulating individual and social behavior.

Table 1. Dynamic model of choice: regression analysis. Given that $Pr(g_1) = 1 - Pr(g_2)$, where $Pr(g_1)$ and $Pr(g_2)$ are the probabilities of choosing gamble 1 and gamble 2, respectively, we define the probability of choosing g_1 in terms of three factors affecting the choice: anticipated disappointment (d), anticipated regret (r), and expected value (e). Let us call x_1, y_1, and x_2, y_2 the two possible outcomes of the first (g_1) and the second (g_2) gambles, respectively, with $x_1 > y_1$, and $x_2 > y_2$. The probability of x_1 is p and the probability of y_1 is $(1 - p)$. The probability of x_2 is q and the probability of y_2 is $(1 - q)$. The model is $Pr(g_{1it}) = F[d_{it}, r_{it}, e_{it}]$, where i is individual and t is time. The function F [θ] denotes the function $\exp(\theta) / [1 + \exp(\theta)]$. The dependent variable, "choice of g_1," is 1 when the subject chooses g_1 and 0 when the subject chooses g_2. Independent variables are d, r, e, where anticipated disappointment choosing g_1, $d = [|y_2 - x_2|\ (1 - q)] - [|y_1 - x_1|\ (1 - p)]$; anticipated regret choosing g_1, $r = [|y_2 - x_1| - |y_1 - x_2|]$; and maximizing expected value choosing g_1, $e = EV(g_1) - EV(g_2) = [p\ x_1 + (1 - p)\ y_1] - [q\ x_2 + (1 - q)\ y_2]$. EV, expected value. Data is from 18 normal control subjects and 5 orbitofrontal patients, in complete feedback condition. Panel logit procedure with individual random effects yields the following results.

Normal control subjects Log likelihood = –211.68417 Wald $chi^2(3)$ = 128.23 Prob > chi^2 = 0.0000					Orbitofrontal patients Log likelihood = –116.60227 Wald $chi^2(3)$ = 54.89 prob > chi^2 = 0.0000				
Variable name	Coefficient	Standard error	z	$P > \|z\|$	Variable name	Coefficient	Standard error	z	$P > \|z\|$
Constant	–.2193792	.145837	–1.50	0.133	Constant	–.4089946	.178328	–2.29	0.022
d	–.001882	.0022904	–0.82	0.411	d	–.0029826	.0030472	–0.98	0.328
r	.0079786	.0016161	4.94	0.000	r	.0019687	.0020464	0.96	0.336
e	.0260426	.0039076	6.66	0.000	e	.0230205	.0049866	4.62	0.000

References and Notes

1. D. Kahneman, D. Miller, *Psychol. Rev.* **93**, 136 (1986).
2. Consider the following example: "Eight years ago a man from Liverpool in UK, committed suicide. He decided to end his life after he knew that he missed out on a £2 million prize in the National Lottery. While watching television he saw the numbers of his winning combination, 14, 17, 22, 24, 42, and 47, appearing one by one on the screen. He always played these numbers, but on this occasion, he had not renewed his ticket on time which actually expired the previous Saturday" (*23*). Although extreme, this example illustrates the profound regret this man felt once he knew the opportunity he missed to become very rich.
3. N. J. Roese, J. M. Olson, *What Might Have Been: The Social Psychology of Counterfactual Thinking* (Erlbaum, Mahwah, NJ, 1995).
4. R. M. J. Byrne, *Trends Cogn. Sci.* **6**, 426 (2002).
5. B. Mellers, I. Ritov, A. Schwartz, *J. Exp. Psychol. Gen.* **3**, 332 (1999).
6. M. Zeelenberg, J. Beattie, J. van der Pligt, N. K. de Vries, *Organ. Behav. Hum. Decis. Process.* **65**, 148 (1996).
7. D. E. Bell, *Oper. Res.* **30**, 961 (1982).
8. G. Loomes, R. Sugden, *Econ. J.* **92**, 805 (1982).
9. E. T. Rolls, *Cereb. Cortex* **10**, 284 (2000).
10. H. C. Breiter, I. Ahron, D. Kahneman, A. Dale, P. Shizgal, *Neuron* **30**, 619 (2001).
11. R. Elliott, J. L. Newman, O. A. Longe, W. J. F. Deakin, *J. Neurosci.* **23**, 303 (2003).
12. L. Tremblay, W. Schultz, *Nature* **398**, 704 (1999).
13. R. J. Dolan, *Science* **298**, 1191 (2002).
14. A. Bechara, A. R. Damasio, H. Damasio, S. W. Anderson, *Cognition* **50**, 7 (1994).
15. V. Goel, J. Grafman, J. Takik, S. Gana, D. Danto, *Brain* **120**, 1805 (1997).
16. A. Bechara, H. Damasio, A. R. Damasio, *Cereb. Cortex* **10**, 295 (2000).
17. Materials and methods are available as supporting material on *Science* Online.
18. Avoiding a loss of 200 changes the negative impact of losing 50 into a neutral affective response. Data for +50 obtained / –200 unobtained versus +50 obtained / –50 unobtained show that the emotional evaluation (elation) is higher in the first case compared with the second one. Thus, the magnitude of the avoided monetary loss does influence emotional response, indicating that relief is present (table S3).
19. J. Von Neumann, O. Morgenstern, *Theory of Games and Economic Behavior* (Princeton University Press, Princeton, NJ, 1944).
20. One could argue that the regret effect is not independent from the disappointment induced by the unobtained outcome of the chosen gamble. However, when reanalyzed as a function of the latter variable (fig. S4), the affective ratings in the complete feedback condition are much less contrasted then when analyzed as a function of the unchosen gamble's outcome.
21. N. H. Frijda, P. Kuipers, E. ter Schure, *J. Pers. Soc. Psychol.* **57**, 212 (1989).
22. M. Zeelenberg, W. W. van Dijk, A. S. R. Manstead, J. Van der Pligt, *Cognition and Emotion* **14**, 521 (2000).
23. M. Zeelenberg, E. van Dijk, in D. Mandel, D. Hilton, P. Catelani, Eds., *The Psychology of Counterfactual Thinking* (Routledge, London, 2004).

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Supporting Online Material

www.sciencemag.org/cgi/content/full/304/5674/1167/DC1
Materials and Methods
Figs. S1 to S4
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References

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Definition of a Bacterial Type IV Secretion Pathway for a DNA Substrate

Eric Cascales and Peter J. Christie*

Bacteria use conjugation systems, a subfamily of the type IV secretion systems, to transfer DNA to recipient cells. Despite 50 years of research, the architecture and mechanism of action of the channel mediating DNA transfer across the bacterial cell envelope remains obscure. By use of a sensitive, quantifiable assay termed transfer DNA immunoprecipitation (TrIP), we identify contacts between a DNA substrate (T-DNA) and 6 of 12 components of the VirB/D4 conjugation system of the phytopathogen *Agrobacterium tumefaciens*. Our results define the translocation pathway for a DNA substrate through a bacterial conjugation machine, specifying the contributions of each subunit of the secretory apparatus to substrate passage.

The translocation of nucleic acids across membrane barriers is central to many cellular processes. Bacterial conjugation systems are a subfamily of the type IV secretion systems (T4SS), which collectively mobilize the transfer of macromolecules such as monomeric proteins, multimeric toxins, and DNA-protein complexes across the cell envelope (*1*, *2*). Conjugation systems mediate horizontal gene transfer, thus contributing to genome plasticity, evolution of infectious pathogens, and dissemination of antibiotic resistance and other virulence traits (*3*). Since the early discovery of the *Escherichia coli* F plasmid transfer system, many regulatory and mechanistic features of this and other T4SS have been described (*1*, *2*, *4*). Surprisingly, however, we still lack a fundamental understanding of the channel through which DNA substrates are delivered across the donor cell envelope.

In nature, *Agrobacterium tumefaciens* uses the VirB/D4 conjugation system (fig. S1) to deliver oncogenic transfer DNA (T-DNA) and effector proteins to susceptible plant cells, often inciting crown gall disease, which can devastate agriculturally important crop species. In the laboratory, the capacity of this bacterium to transfer DNA between kingdom boundaries has been exploited to genetically engineer a large number of plant, fungal, and other eukaryotic species (*5*). Here, we sought to define the translocation route for the T-DNA through this archetypal T4SS (*1*).

We developed a sensitive assay termed transfer DNA immunoprecipitation (TrIP) to identify close contacts between the T-DNA substrate as it exits the cell and subunits of the VirB/D4 T4SS (*6*) (fig. S2). This assay was adapted from the chromatin immunoprecipitation (ChIP) assay commonly used to study chromatin and transcription complexes in eukaryotic cells (*7*). In this three-stage assay, we treat *vir* gene–induced *A. tumefaciens* cells with formaldehyde to cross-link proteins to DNA in vivo, and then we precipitate a Vir protein of interest from detergent-solubilized cell extracts. Finally, we assay for coprecipitation of DNA by the polymerase chain reaction (PCR). We amplify DNA with two sets of primers, one specific for the left end of the transmissible T_L-DNA carried on the tumor-inducing (Ti) plasmid pTiA6NC of strain A348. The second set is specific for the nontransferred octopine catabolism region (*ophDC*) positioned ~25 kb from the T-DNA on the Ti plasmid. We further developed a quantitative version of TrIP to compare levels of DNA substrate recovered in the immunoprecipitates (fig. S3).

Initially, we defined the genetic requirements for two early reactions associated with type IV translocation: substrate processing and recruitment to the secretory apparatus. Reminiscent of the processing of conjugative plasmids (*8*), the *A. tumefaciens* VirD2 relaxase binds origin of transfer–like T-DNA border sequences and cleaves the strand destined for transfer (T-strand). The relaxase is thought to remain covalently bound to the 5′ end of the T-strand, resulting in a VirD2–T-strand nucleoprotein particle. We isolated this presumptive transfer intermediate by immunoprecipitation with antibodies to VirD2 (Fig. 1A). The antibodies precipitated VirD2 as well as the T-strand—but not the *ophDC* Ti plasmid control fragment—from extracts of wild-type cells as well as mutants (table S1) defective for synthesis of the secretory

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