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## Deciding Advantageously Before Knowing the Advantageous Strategy

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Deciding advantageously in a complex situation is thought to require overt reasoning on declarative knowledge, namely, on facts pertaining to premises, options for action, and outcomes of actions that embody the pertinent previous experience. An alternative possibility was investigated: that overt reasoning is preceded by a nonconscious biasing step that uses neural systems other than those that support declarative knowledge. Normal participants and patients with prefrontal damage and decision-making defects performed a gambling task in which behavioral, psychophysiological, and self-account measures were obtained in parallel. Normals began to choose advantageously before they realized which strategy worked best, whereas prefrontal patients continued to choose disadvantageously even after they knew the correct strategy. Moreover, normals began to generate anticipatory skin conductance responses (SCRs) whenever they pondered a choice that turned out to be risky, before they knew explicitly that it was a risky choice, whereas patients never developed anticipatory SCRs, although some eventually realized which choices were risky. The results suggest that, in normal individuals, nonconscious biases guide behavior before conscious knowledge does. Without the help of such biases, overt knowledge may be insufficient to ensure advantageous behavior.

In a gambling task that simulates real-life decision-making in the way it factors uncertainty, rewards, and penalties, the players are given four decks of cards, a loan of \$2000 facsimile U.S. bills, and asked to play so that they can lose the least amount of money and win the most (1). Turning each card carries an immediate reward (\$100 in decks A and B and \$50 in decks C and D). Unpredictably, however, the turning of some cards also carries a penalty (which is large in decks A and B and small in decks C and D). Playing mostly from the disadvantageous decks (A and B) leads to an overall loss. Playing from the advantageous decks (C and D) leads to an

overall gain. The players have no way of predicting when a penalty will arise in a given deck, no way to calculate with precision the net gain or loss from each deck, and no knowledge of how many cards they must turn to end the game (the game is stopped after 100 card selections). After encountering a few losses, normal participants begin to generate SCRs before selecting a card from the bad decks (2) and also begin to avoid the decks with large losses (1). Patients with bilateral damage to the ventromedial prefrontal cortices do neither (1, 2).

To investigate whether subjects choose correctly only after or before conceptualizing the nature of the game and reasoning over the pertinent knowledge, we continuously assessed, during their performance of the task, three lines of processing in 10 normal participants and in 6 patients (3) with bilateral damage of the ventromedial sector of the prefrontal cortex and decision-making defects. These included (i) behavioral performance, that is, the number of cards selected from the

good decks versus the bad decks; (ii) SCRs generated before the selection of each card (2); and (iii) the subject's account of how they conceptualized the game and of the strategy they were using. The latter was assessed by interrupting the game briefly after each subject had made 20 card turns and had already encountered penalties, and asking the subject two questions: (i) "Tell me all you know about what is going on in this game." (ii) "Tell me how you feel about this game." The questions were repeated at 10-card intervals and the responses audiotaped.

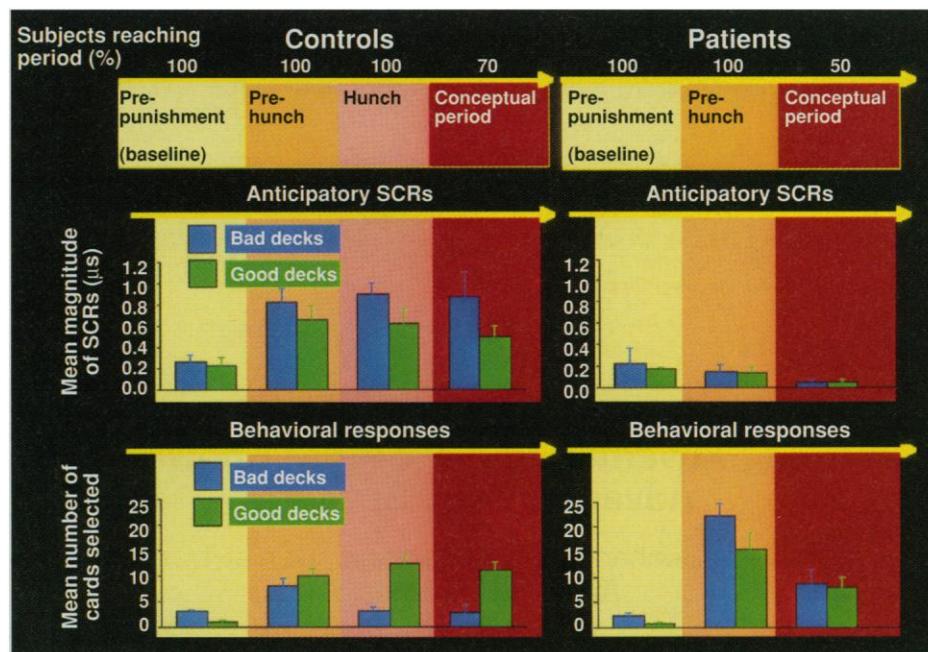
After sampling all four decks, and before encountering any losses, subjects preferred decks A and B and did not generate significant anticipatory SCRs. We called this period pre-punishment. After encountering a few losses in decks A or B (usually by card 10), normal participants began to generate anticipatory SCRs to decks A and B. Yet by card 20, all indicated that they did not have a clue about what was going on. We called this period pre-hunch (Fig. 1). By about card 50, all normal participants began to express a "hunch" that decks A and B were riskier and all generated anticipatory SCRs whenever they pondered a choice from deck A or B. We called this period hunch. None of the patients generated anticipatory SCRs or expressed a "hunch" (Fig. 1). By card 80, many normal participants expressed knowledge about why, in the long run, decks A and B were bad and decks C and D were good. We called this period conceptual. Seven of the 10 normal participants reached the conceptual period, during which they continued to avoid the bad decks, and continued to generate SCRs whenever they considered sampling again from the bad decks. Remarkably, the three normal participants who did not reach the conceptual period still made advantageous choices (4). Just as remarkably, the three patients with prefrontal damage who reached the conceptual period and correctly described which were the bad and good decks chose disadvantageously. None of the patients generated anticipatory SCRs (Fig. 1). Thus, despite an accurate account of the task and of the correct strategy, these patients failed to generate au-

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**Fig. 1.** Presentation of the four periods in terms of average numbers of cards selected from the bad decks (A and B) versus the good decks (C and D), and the mean magnitudes of anticipatory SCRs associated with the same cards. The pre-punishment period covered the start of the game when subjects sampled the decks and before they encountered the first loss (that is, up to about the 10th card selection). The pre-hunch period consisted of the next series of cards when subjects continued to choose cards from various decks, but professed no notion of what was happening in the game (on average, between the 10th (range: 7 to 13) and the 50th card (range: 30 to 60) in normals, or between the 9th (3 to 10) and the 80th card (60 to 90) in patients). The hunch period (never reached in patients) corresponded to the period when subjects reported “liking” or “disliking” certain decks, and “guessed” which decks were risky or safe, but were not sure of their answers [on average, between the 50th (30 to 60) and 80th card (60 to 90) in normals]. The conceptual period corresponded to the period when subjects were able to articulate accurately the nature of the task and tell for certain which were the good and bad decks, and why they were good or bad [on average, after the 80th card (60 to 90) in both normals and patients]. (Top panels) Bars represent means ( $\pm$ SEM) of the mean magnitude of anticipatory SCRs generated before the selection of cards from the bad decks versus the good decks. Anticipatory SCRs are generated in the time window before turning a card from any given deck, that is, during the time the subject ponders from which deck to choose (2). SCRs in association with the good and bad decks from normal controls or patients were not significantly different during the pre-punishment (baseline) period. However, there was a significant increase in the magnitude of these



SCRs during the pre-hunch period, but only for normal controls. During the next two periods, SCR activity in normal subjects was sustained in the case of the bad decks, but it began to subside in the case of the good decks (8). (Bottom panels) Bars in the “Behavioral responses” plots represent means ( $\pm$ SEM) of the mean number of cards selected from the bad decks versus those selected from the good decks. Normal controls selected more cards from the good decks during the pre-hunch, hunch, and conceptual periods. In contrast, prefrontal patients selected more cards from the bad decks during these periods (9).

tonomic responses and continued to select cards from the bad decks. The patients failed to act according to their correct conceptual knowledge.

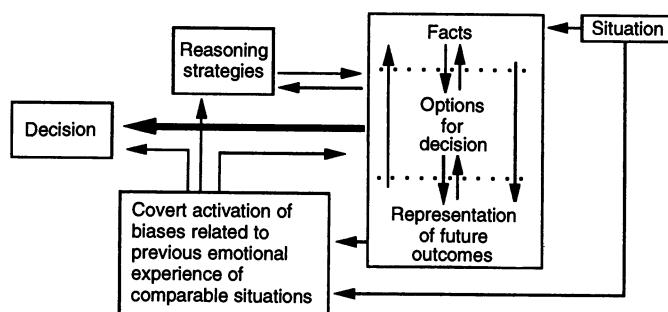
On the basis of these results, we suggest that the sensory representation of a situation that requires a decision leads to two largely parallel but interacting chains of events (Fig. 2). In one, either the sensory representation of the situation or of the facts evoked by it activate neural systems that hold nondeclarative dispositional knowledge related to the individual’s previous emotional experience of similar situations (5). The ventromedial frontal cortices are among the structures that we suspect hold such dispositional knowledge, the activation of which, in turn, activates

autonomic and neurotransmitter nuclei (such as those that deliver dopamine to selected cortical and subcortical forebrain regions), among other regions. The ensuing nonconscious signals then act as covert biases on the circuits that support processes of cognitive evaluation and reasoning (6). In the other chain of events, the representation of the situation generates (i) the overt recall of pertinent facts, for example, various response options and future outcomes pertaining to a given course of action; and (ii) the application of reasoning strategies to facts and options. Our experiment indicates that in normal participants, the activation of covert biases preceded overt reasoning on the available facts. Subsequently, the covert biases may

have assisted the reasoning process in cooperative manner, that is, biases would not decide per se, but rather facilitate the efficient processing of knowledge and logic necessary for conscious decisions (7). We suspect that the autonomic responses we detected are evidence for a complex process of nonconscious signaling, which reflects access to records of previous individual experience—specifically, of records shaped by reward, punishment, and the emotional state that attends them. In this light, damage to ventromedial cortices acts by precluding access to a particular kind of record of previous and related individual experience.

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3. The patients who participated in the experiment were drawn from the Division of Cognitive Neuroscience’s Patient Registry and have been described previously (1, 2). Three are female (ages 53, 63, and 64), and three are male (ages 51, 52, and 65). All have stable focal lesions. Years of education:  $13 \pm 2$  (mean  $\pm$  SEM); verbal IQ:  $111 \pm 8$  (mean  $\pm$  SEM); performance IQ:  $102 \pm 8$  (mean  $\pm$  SEM).
4. The results in this group of normal participants are similar to the results described previously in other normal participants (2).
5. A. R. Damasio, *Descartes’ Error: Emotion, Reason, and the Human Brain* (Grosset/Putnam, New York, 1994).
6. We envision these biases to act as markers or qualifiers in the manner suggested by A. Damasio [in (5), chap. 8] and by A. R. Damasio, D. Tranel, and H. Damasio [in



**Fig. 2.** Diagram of the proposed steps involved in decision-making.

# Single Molecule Force Spectroscopy on Polysaccharides by Atomic Force Microscopy

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Recent developments in piconewton instrumentation allow the manipulation of single molecules and measurements of intermolecular as well as intramolecular forces. Dextran filaments linked to a gold surface were probed with the atomic force microscope tip by vertical stretching. At low forces the deformation of dextran was found to be dominated by entropic forces and can be described by the Langevin function with a 6 angstrom Kuhn length. At elevated forces the strand elongation was governed by a twist of bond angles. At higher forces the dextran filaments underwent a distinct conformational change. The polymer stiffened and the segment elasticity was dominated by the bending of bond angles. The conformational change was found to be reversible and was corroborated by molecular dynamics calculations.

Recently a series of single molecule experiments provided detailed insight into intermolecular and intramolecular forces, providing relevant information on molecular mechanisms (1–4). In previous experiments we and others chemically linked molecular pairs such as biotin and avidin (3, 5), or conjugated DNA strands (6), between the tip of an atomic force microscope (AFM) cantilever and support structures. Molecule-specific bond forces between binding pairs were measured upon separation and compared with known thermodynamic parameters (4). Here we used this approach to probe elastic properties of single polymer strands.

The experimental geometry is depicted in Fig. 1A. Dextran (average molecular weight 500,000) linked to a gold surface through epoxy-alkanethiols were activated with one carboxymethyl group per glucose unit on average (7) and reacted with streptavidin such that several molecules were chemically bound to each dextran filament (Sensor Chip SA5, Pharmacia Biosensor AB, Uppsala, Sweden). The mean distance between the grafting points of two different polymer strands was about 200 Å, and the hydrated “polymer brush” extended 1000 to 2000 Å into the solution (7). Because in physiological buffer dextran behaves like an ideal polymer, the coil overlap is expected to be low. In our experiments streptavidin served as a molecular handle for the manipulation of the polymer to be investigated. An AFM cantilever with biotin bound to the AFM tip, following the protocol given in (3), was used to pull on individual dextran filaments through the biotin-streptavidin bond (8). To minimize

the number of multiple bonds, which typically occur when the tip penetrates the polymer brush, we let the tip approach and retract step by step without it indenting into the sample until a binding event was registered. In this “fly fishing mode” the undesirable multiple bonds can be efficiently avoided (9). Alternatively, one can “manually” disentangle an individual filament from the polymer brush by slowly pulling back the tip while monitoring all multiple bonds and tangles rupturing until just one last filament is stretched (see the first trace of Fig. 4, discussed further below). This filament can then be repeatedly manipulated as long as the force is kept below the force limit of the molecular handles.

Several measured elongation curves of dextran strands of various lengths are shown in Fig. 1B (10). At the given extension rate of 0.5 μm/s the biotin-streptavidin bond is known to hold up to a force  $F$  of  $250 \pm 25$  pN (4). The measured deformation curves were modeled by entropy springs with segment elasticity (11). Although the contour lengths  $L_{\text{contour}}$  of the polymers varied from 0.4 to 1.6 μm, the measured Kuhn length  $l_K = 6 \pm 0.5$  Å and the segment elasticity  $k_{\text{segment}} = 670 \pm 100$  pN/Å showed only marginal variation between the filaments. This result was reproduced for several hundred filaments that were measured with different cantilevers in different experiments (12). The finding that the segment elasticity and Kuhn length are virtually identical for all measured dextran strands confirms that predominantly individual filaments are measured by this method and that the deformation of the couplers is negligible at polysaccharide lengths greater than 2000 Å (13).

An interpretation of the measured segment elasticity is given by molecular dynamics (MD) calculations. These reveal that at low forces the main contribution of the elasticity stems from a twist of the C5–C6 bond

- Frontal Lobe Function and Dysfunction*, H. S. Levin, H. M. Eisenberg, A. L. Benton, Eds. (Oxford Univ. Press, New York, 1991), pp. 217]. See also P. R. Montague, P. Dayan, C. Person, T. J. Sejnowski, *Nature* **377**, 725 (1995). This action might occur both at the cortical level and in subcortical structures such as basal ganglia.
- On the basis of a series of related studies [A. Bechara, D. Tranel, H. Damasio, S. W. Anderson, A. R. Damasio, *Soc. Neurosci. Abstr.* **21**, 1210 (1995); D. Tranel, A. Bechara, H. Damasio, A. R. Damasio, *ibid.* **22**, 1108 (1996)], we believe that the bias mechanism identified here is distinct from other neural mechanisms whose integrity is crucial for decision-making. Such mechanisms include response inhibition [J. M. Fuster, *The Prefrontal Cortex: Anatomy, Physiology, and Neuropsychology of the Frontal Lobe* (Raven, New York, ed. 3, 1996); R. Dias, T. W. Robbins, A. C. Roberts, *Nature* **380**, 69 (1996); A. Diamond, in *The Development and Neural Bases of Higher Cognitive Functions*, A. Diamond, Ed. (New York Academy of Sciences, New York, 1990), vol. 608, pp. 637–669], working memory [P. S. Goldman-Rakic, in *Handbook of Physiology; The Nervous System*, F. Plum, Ed. (American Physiological Society, Bethesda, MD, 1987), vol. 5, pp. 373–401], and selective attention [M. I. Posner and S. Dehaene, *Trends Neurosci.* **17**, 75 (1994)]. In other words, we propose an addition to mechanisms already recognized as necessary for proper reasoning rather than an alternative to those mechanisms.
  - A three-way analysis of variance (ANOVA) on the anticipatory SCRs generated by normal participants and patients (between group), during the pre-punishment and pre-hunch periods (within group), and in association with the bad and good decks (within group) revealed, most importantly, a significant two-way interaction of group with period [ $F(1,14) = 16.24$ ,  $P < 0.001$ ]. Subsequent Newman-Keuls tests on these SCRs revealed that, during the pre-punishment (baseline) period, the SCRs associated with the good or bad decks of normals or patients were not significantly different. However, there was a significant increase in the magnitude of these SCRs during the pre-hunch period, relative to the pre-punishment period, but only for normals ( $P < 0.01$ ). The SCRs from normals during pre-hunch were also significantly higher than the SCRs of patients during both pre-punishment and pre-hunch ( $P < 0.01$ ). Because all normals generated anticipatory SCRs, whereas all patients did not, Fisher's exact test, based on the hypergeometric distribution, yielded a one-sided  $P < 0.001$ . SCRs from normals who selected cards from the bad decks during the hunch period were compared to the SCRs associated with sampling the good decks. The same comparisons of SCRs were done for the conceptual period. Although SCRs from the bad decks during the hunch or the conceptual period were generally higher than those from the good decks, the difference did not reach statistical significance. However, Newman-Keuls tests comparing SCRs from the hunch or the conceptual period to those from the pre-punishment period revealed significant differences in the case of the bad decks ( $P < 0.01$ ) but not the good decks. This suggests that SCR activity was sustained in the case of the bad decks, but may have been subsiding in the case of the good decks.
  - A similar ANOVA in which mean number of cards selected was used instead of SCRs revealed, most importantly, a significant three-way interaction of group with period with decks [ $F(1,14) = 6.9$ ,  $P < 0.02$ ]. With subsequent Newman-Keuls tests, the most relevant comparison was that patients selected significantly more cards from the bad decks relative to the good decks during the pre-hunch period ( $P < 0.01$ ). By contrast, controls selected more from the good decks relative to the bad decks (the difference was not statistically significant). During the hunch and conceptual periods, controls selected significantly more cards from the good decks relative to the bad decks ( $P < 0.01$ ). By contrast, patients still selected more cards from the bad decks relative to the good decks during the conceptual period (the difference was not statistically significant).
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