

Diminishing Reciprocal Fairness by Disrupting the Right Prefrontal Cortex

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Humans restrain self-interest with moral and social values. They are the only species known to exhibit reciprocal fairness, which implies the punishment of other individuals' unfair behaviors, even if it hurts the punisher's economic self-interest. Reciprocal fairness has been demonstrated in the Ultimatum Game, where players often reject their bargaining partner's unfair offers. Despite progress in recent years, however, little is known about how the human brain limits the impact of selfish motives and implements fair behavior. Here we show that disruption of the right, but not the left, dorsolateral prefrontal cortex (DLPFC) by low-frequency repetitive transcranial magnetic stimulation substantially reduces subjects' willingness to reject their partners' intentionally unfair offers, which suggests that subjects are less able to resist the economic temptation to accept these offers. Importantly, however, subjects still judge such offers as very unfair, which indicates that the right DLPFC plays a key role in the implementation of fairness-related behaviors.

Across species, humans have been spectacularly successful in limiting the impact of self-interest even in interactions between genetically unrelated strangers, by developing and enforcing social norms (1, 2). Fairness norms, in particular, play a crucial role in social life across many cultures (3). They are enforced by reciprocally fair behaviors, which imply that kind acts are reciprocated with kindness, whereas hostile or unfair acts are reciprocated with hostility (4). The role of fairness also has been acknowledged in formal theories of reciprocal fairness (henceforth, "reciprocity") (4) and inequity aversion (5), both of which assume that people trade off fairness goals against the goal of increasing their material resources.

The Ultimatum Game (6) illustrates the tension between economic self-interest, on the one hand, and reciprocity and equity motives, on the other. In this game, two anonymous individuals, a proposer and a responder, have to agree on the division of a given amount of money, say \$20, according to the following rules: The proposer can make exactly one suggestion on how the \$20 should be allocated between the two by making an integer offer X to the responder. Then the responders can either accept or reject X . In case of a rejection, both players earn \$0; in case of acceptance, the responder earns X and the proposer earns $20 - X$. If economic self-interest alone motivates the responder, he will accept even a very low offer, say \$1, because \$1 is better than \$0. However, if concerns for reciprocity and equity motivate him, he might reject low offers because he views them as

insultingly unfair and inequitable. The responder thus faces a conflict in case of low offers between his economic self-interest, which encourages him to accept the offer, and his fairness goals, which drive him toward rejecting it.

Strong evidence (3, 7) suggests that many people reject low offers in the game, even if stake levels are as high as 3 months' income (8). Rejection rates up to 80% have been observed (7) for offers below 25% of the available money, and a pioneering imaging study (9) showed that both the anterior insula—an important brain area involved in the processing of emotions (10)—and the dorsolateral prefrontal cortex (DLPFC) are activated when responders decide whether to accept or reject an unfair offer. The fact that both the right and left DLPFCs are more strongly activated when subjects face unfair offers compared with when they face fair offers is of particular interest for our purposes. The DLPFC is widely thought to be involved in executive control, goal maintenance, and the inhibition of

prepotent responses (11). All of these functions are relevant for the responder in the Ultimatum Game, because there are likely to be several competing goals—fairness goals and self-interest—and the questions are as follows: Which of them should be maintained, i.e., given priority, and which motivational impulse should be restrained?

One plausible hypothesis about the role of the DLPFC is that unfair offers generate an impulse to reject, and that DLPFC activity is involved in controlling this impulse (9). According to this hypothesis, DLPFC activity is involved in the cognitive control of the emotional impulse associated with fairness goals. A contrasting but equally plausible hypothesis is that fundamental impulses associated with self-interest need to be controlled in order to maintain and to implement culture-dependent fairness goals (3). According to this hypothesis, the DLPFC is involved in overriding selfish impulses, the latter of which may also be strongly associated with emotional forces. This second hypothesis has a "Freudian" flavor because Freud's theory of the ego and the superego is based on the assumption that the ego and the superego need to override the fundamentally selfish nature of the id in order for human beings to behave in reasonable and morally appropriate ways (12). Both hypothesis are, however, consistent with dual-systems approaches (13–16) that stress the fundamental differences between emotional (impulsive) and deliberative systems, or between automatic and controlled processes, because both fairness and selfish impulses may have strong emotional content.

If we suggest that DLPFC may be involved in inhibiting or overriding self-interest motives, we do not want to imply that DLPFC directly suppresses other brain areas that represent self-interest. Rather the term "inhibition" is a convenient short term for top-down control (or executive control), whose overall effect is a reduction in the weight

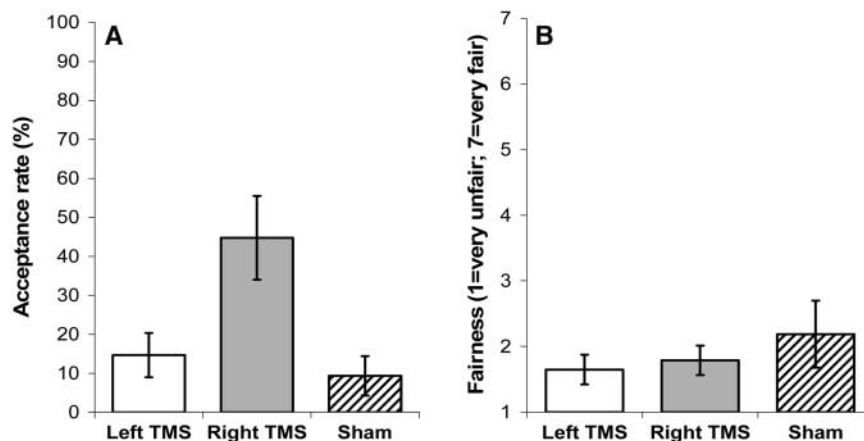


Fig. 1. Behavioral responses and fairness judgments (means \pm SEM) related to the most unfair offer of CHF 4 in the human offer condition. **(A)** Acceptance rates across treatment groups. Subjects whose right DLPFC is disrupted exhibit a much higher acceptance rate than those in the other two treatment groups (Mann-Whitney U tests, two-tailed, $P < 0.05$). **(B)** Perceived unfairness across treatments (1 = very unfair; 7 = very fair). Subjects in all three treatment groups perceive an offer of 4 as very unfair, and there are no significant differences across groups.

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of self-interested impulses on an individual's action. Thus, rather than directly suppressing neural activities that represent self-interested impulses, the DLPFC may be part of a network that modulates the relative impact of fairness motives and self-interest goals on decision-making. The final outcome of this modulation may then be a weakening of the impact of self-interest motives on decision-making.

The fact that the DLPFC is more strongly activated with unfair offers than with fair ones (9) does not necessarily mean that this brain region is crucially involved in the implementation of fair behaviors. In principle, it is even possible that DLPFC activation is not causally involved in the decision to accept or reject unfair offers, but instead, represents only a by-product of some other process. In order to examine whether DLPFC activity is crucial in the responders' decisions and to discriminate between the two hypotheses mentioned above, we applied low-frequency repetitive transcranial magnetic stimulation (rTMS) to 52 subjects in the role of the responder in an anonymous Ultimatum Game with a stake size of Swiss francs (CHF) 20 (CHF 1 \approx \$0.80). We limited the proposer's strategy space by only permitting offers of CHF 10, 8, 6, or 4 (17) in order to generate enough observations on the responders' side. CHF 10 is obviously the fairest offer, because it splits the stake size equally, whereas CHF 4 is the most unfair offer. Each responder played the Ultimatum Game 20 times with 20 different anonymous partners. In order to investigate a possible hemispheric laterality in the role of DLPFC on responders' decisions, we applied low-frequency rTMS for 15 min to the right (19 subjects) or to the left DLPFC (17 subjects). Low-frequency rTMS for the duration of several minutes leads to a suppression of activity in the stimulated brain region that outlasts the duration of the rTMS train for about half the duration of the stimulation. The existence of a group that receives rTMS to the right DLPFC and a control group that receives rTMS to the left DLPFC is also important because this controls for the potential side effects of rTMS (18, 19), including discomfort, irritation, and mood changes. In addition, we had a further control condition where we applied sham stimulation for 15 min to the right or left DLPFC (16 subjects). Each subject participated in only one of the three conditions (left stimulation, right stimulation, or sham), and none had experienced TMS previously. This is important because subjects who experienced real rTMS before or after sham stimulation on the same day are very likely to be able to distinguish between the two stimulations (17), which questions the control status of the sham stimulation. Therefore, a pioneering attempt (20), which lacked an active rTMS control stimulation and an across-subject sham control, could not attribute possible behavioral changes associated with low-frequency rTMS to the disruption of DLPFC.

How will the disruption of DLPFC with low-frequency rTMS affect the responders' behavior? If the DLPFC is involved in implementing fair behavior, which requires overriding selfish impulses, disrupting this brain region should increase the acceptance rate for unfair offers relative to the sham-stimulation condition. In other words, if we disrupt activity in a brain region hypothesized to place controls on selfish impulses, we should functionally weaken the control, and selfish impulses should thus have a stronger impact on decision-making; the acceptance rate of unfair offers should, therefore, increase. Alternatively, if DLPFC activity is involved in the cognitive control associated with the inhibition of fairness impulses, low-frequency rTMS applied to this brain area should reduce the acceptance rate of unfair offers, because the fairness impulses should affect behavior more strongly if the ability to inhibit them is reduced. Thus, the two hypotheses make opposite predictions on how low-frequency rTMS of DLPFC affects acceptance rates relative to the sham stimulation.

The application of rTMS to the right and left DLPFC also enables us to test a lateralization hypothesis. A number of studies have reported preferential right-hemispheric involvement in the inhibitory control of behavior (21–24). This has been shown in go/no-go tasks (21, 22) and risky choice tasks (24), for example, and there appears to be a right hemispheric lateralization of syndromes, in which impairments in decision-making and social behavior seem to reflect a breakdown of control processes (25). We, therefore, conjectured that disruption of the right DLPFC might be associated with different effects compared with the disruption of the left DLPFC.

In addition to the conditions (left DLPFC, right DLPFC, or sham) mentioned above, we also implemented the following treatment variation. In each of the three conditions, a responder played 10 games with partners who were responsible for their offers, because they decided how much to offer (human-offer condition), as well as 10 games with partners who were not responsible for their offers because a computer

randomly generated the offers (computer-offer condition). The latter condition is interesting because previous evidence indicates (26) that two fairness motives—reciprocity (4) and inequity aversion (5)—are simultaneously activated in the human-offer condition, whereas only one fairness motive—inequity aversion—is operative in the computer-offer condition. A responder motivated by reciprocity rejects a low offer because he wants to punish the proposer's unfair behavior, whereas the inequity aversion motive is characterized by resistance against the unfair distribution of income that results from a low offer, no matter how this distribution was generated. Therefore, the motive to punish the partner for an unfair offer cannot play a role in the computer-offer condition, because the partner is not responsible for it. As a consequence, the behavioral impact of rTMS in the computer-offer condition enables us to specify the interpretation of our results by comparing the effects of the disruption of the DLPFC in situations where the reciprocity motive is present and absent.

As expected, the acceptance rates varied strongly across offers. In the human-offer condition, offers of 4 were accepted on average in 24% of the trials, whereas the acceptance rate for offers of 6 was 67%, and offers of 8 were accepted in 99% of the cases. For our purposes, acceptance behavior with regard to the lowest offers is most interesting, because the tension between fairness and self-interest is greatest in this case. After sham rTMS, the acceptance rate for the most unfair offer was 9.3% and after real rTMS of the left DLPFC it was 14.7% (Fig. 1A). These results contrast sharply with the acceptance rate of 44.7% after rTMS of the right DLPFC. In fact, 37% of the subjects accepted all unfair offers after right DLPFC disruption, whereas no subjects in the sham or the left DLPFC group accepted all of them. The differences across all three groups are significant (Kruskal-Wallis test, $H = 7.265$, $df = 2$, $n = 52$, $P = 0.026$), and pairwise two-tailed Mann-Whitney U tests confirm that the right DLPFC group has a significantly higher acceptance rate

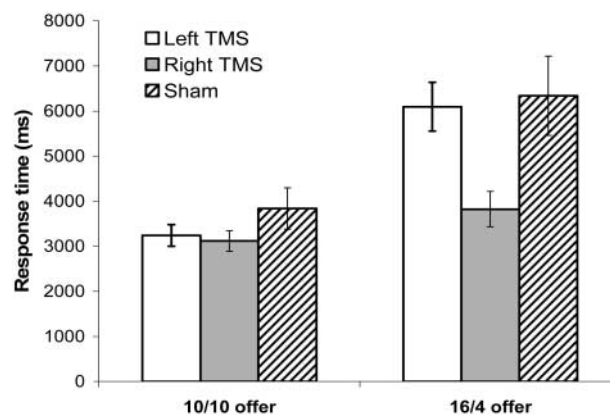


Fig. 2. Response times for fair and unfair offers in the human offer condition. If subjects face a fair offer of 10 they quickly accept the offer, and there are no significant differences across treatment groups (Kruskal-Wallis test, $P = 0.264$). If subjects face an unfair offer of 4 the response time strongly increases for subjects whose left DLPFC is disrupted and for those who receive sham stimulation. However, subjects whose right DLPFC is disrupted accept unfair offers almost as quickly

than either the left DLPFC ($Z = -1.969$, $n = 36$, $P = 0.049$) or the sham group ($Z = -2.388$, $n = 35$, $P = 0.017$). The same results hold if we pool the behavioral responses to unfair offers of 4 and 6 and conduct a repeated measures analysis of variance (ANOVA) of treatment (left DLPFC, right DLPFC, or sham) \times offer (4, 6). We find a main effect of treatment [$F(42,49) = 5.30$, $P = 0.008$], and Fisher's post hoc test demonstrates that subjects who received rTMS over right DLPFC were more likely to accept offers of 4 or 6 than those stimulated over left DLPFC ($P = 0.041$) or those who received sham rTMS ($P = 0.003$). Interestingly, we found no interaction effect of treatment \times offer ($P = 0.398$), which indicated that subjects' acceptance behavior shows a similar pattern for both unfair offers (i.e., higher acceptance rate after right DLPFC disruption compared with the other two conditions).

These differences across conditions can neither be attributed to different propensities to behave reciprocally nor to differences in individual impulsivity across treatment groups. Roughly 10 days after the experiment, the subjects also completed personality questionnaires that assessed their impulsivity (27) and propensity to reciprocate (17, 28). We observed no differences across treatment groups for either impulsivity (Kruskal-Wallis test, $H = 3.693$, $df = 2$, $P = 0.158$) or reciprocity (Kruskal-Wallis test, $H = 0.853$, $df = 2$, $P = 0.653$). Moreover, the treatment differences in acceptance rates remain highly significant if we control for individuals' impulsivity and reciprocity scores in a repeated measures ANOVA [main effect of treatment ($F = 4.701$, $P = 0.014$); Fisher's post hoc test: right versus left DLPFC ($P = 0.020$), right versus sham ($P = 0.007$)].

Interestingly, although rTMS of the right DLPFC reduced the rejection rate, rTMS did not change subjects' fairness judgments. We

elicited subjects' fairness judgments with regard to different offers on a seven-point scale (17) immediately after the Ultimatum Game experiment. Subjects in all three treatment groups judged the lowest offer of 4 as rather unfair when the human partner made this offer (Fig. 1B), and a Kruskal-Wallis test indicated no differences in fairness judgments across treatments ($H = 0.197$, $df = 2$, $P = 0.911$). Similarly, there were also no differences in the fairness assessment of offers of 6 across treatments ($H = 0.487$, $df = 2$, $P = 0.784$). Thus, disruption of the right DLPFC diminishes fair behavioral responses to low offers but does not affect subjects' fairness judgments.

The results reported above support the hypothesis that right, but not left, DLPFC activity, is crucial for the ability to override selfish impulses in order to reject offers perceived as unfair. The response-time difference for accepted unfair and fair offers across groups provides further support for this hypothesis (Fig. 2). If subjects face a fair offer of 10 they quickly accept, and no response-time differences across treatment groups are observed (Kruskal-Wallis test, $H = 2.662$, $df = 2$, $P = 0.264$). In sharp contrast, subjects who receive rTMS to the left DLPFC or sham stimulation need much longer to accept unfair offers of 4 than subjects who receive fair offers, which suggests that there is a conflict between self-interest and fairness motives at unfair offers that causes an increase in response time. However, subjects whose right DLPFC is disrupted exhibit similar response times for both fair and unfair offers (Fig. 2). Thus, large and significant differences across treatment groups occurred at offers of 4 (Kruskal-Wallis test, $H = 8.051$, $df = 2$, $P = 0.0179$); subjects in the right DLPFC group accepted unfair offers significantly faster than do subjects in the left DLPFC group (Mann-Whitney U test, two-tailed, $P = 0.018$) or in the sham

group (Mann-Whitney U test, two-tailed, $P = 0.028$). In terms of response time, subjects with right DLPFC disruption seem to be less able to resist the selfish temptation to accept low offers although they view them as unfair.

The hypothesis that right DLPFC is crucial in implementing fairness behaviors by overriding self-interested impulses also has implications for the computer-offer condition. Recall that the motive for punishing the partner for unfair offers cannot play a role in this condition, because the partner is not responsible for the offers. As a consequence, the fairness forces are weak, and therefore, the effects of disrupting the ability to implement fair behaviors should also be so. This pattern contrasts with the human-offer condition where the fairness forces are strong; disruption of the ability to implement fair actions should, therefore, have a strong impact on behavior. Thus, the hypothesis that right DLPFC is crucial for the ability to implement fairness goals predicts that disruption of the right DLPFC activity will generate weaker effects in the computer-offer condition than in the human-offer condition.

The data indeed support this prediction. The average acceptance rate of an offer of 4 was 67.3% in the computer-offer condition, which was much higher than the 24% in the human-offer condition. The fact that fairness forces were weaker in the computer-offer condition is also indicated by the perceived unfairness of an offer of 4 (compare Fig. 3B with Fig. 1B) but, as in the human-offer condition, there were no differences in the perceived unfairness across treatment groups (Kruskal-Wallis test, $H = 0.052$, $P = 0.974$). In contrast to the human-offer condition there were no significant differences in acceptance rates across left DLPFC, right DLPFC, and sham condition (Fig. 3A; Kruskal-Wallis test, $H = 2.370$, $P = 0.306$), which suggests that the disruption of right DLPFC has no, or only minor, effects in the computer-offer condition. A similar conclusion was suggested by a repeated measures ANOVA, which indicated an interaction between treatment type (i.e., human- versus computer-offer condition) and treatment group (i.e., left DLPFC, right DLPFC, or sham condition) ($F = 3.318$, $P = 0.045$). This shows that the computer-offer condition significantly reduces the behavioral differences across treatment groups relative to the human-offer condition.

These findings illustrate the importance of rTMS for progress in understanding the neural basis of human decision-making. First, previous neuroimaging studies (9) put forward the view that the DLPFC is crucial in overriding or weakening self-interested impulses and thus enables subjects to implement their fairness goals. Subjects are much more willing to behave selfishly, i.e., to accept unfair offers, after disruption of the right DLPFC. In addition, they accept unfair offers almost as quickly as fair-of-

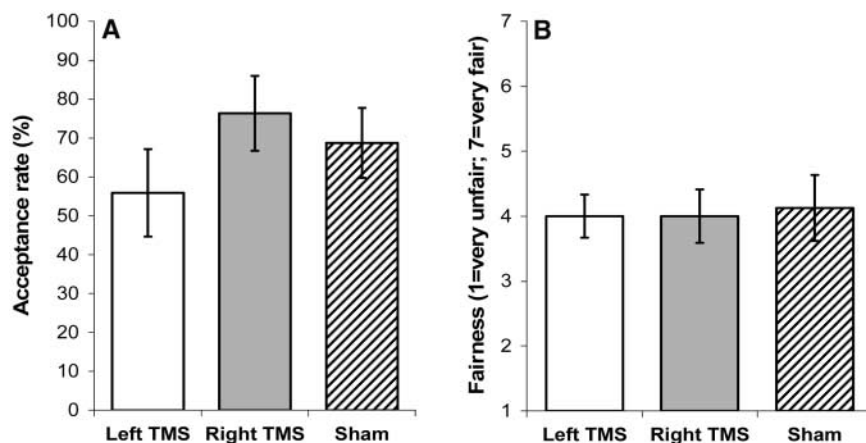


Fig. 3. Behavioral responses and fairness judgments (means \pm SEM) related to the most unfair offer of CHF 4 in the computer offer condition. (A) Acceptance rates across treatment groups. The differences across treatment groups are not significant, and they are significantly smaller than in the human offer condition (repeated measures ANOVA, $P < 0.05$). (B) Perceived unfairness across treatments (1 = very unfair; 7 = very fair). Subjects in all three treatment groups perceive an offer of 4 as less unfair than in the human offer condition (compare with Fig. 1B), and there are no differences in fairness judgments across treatment groups.

fers, which suggests that self-interest impulses have a stronger impact on behavior. Second, our rTMS study also enables us to claim a causal role of DLPFC activity in the implementation of fairness motives when self-interest and fairness are in conflict. The only previous attempt (20) could not attribute a weak behavioral effect of rTMS to the disruption of DLPFC because it used a confounded sham control and lacked an active rTMS control stimulation (29). Third, disruption of right DLPFC activity only affects fairness-related behaviors but not fairness judgments. Subjects behave as if they can no longer implement their fairness goals after disruption of the right DLPFC. This finding is also interesting in light of evidence suggesting that patients with right prefrontal lesions are characterized by the inability to behave in normatively appropriate ways, despite the fact that they have the judgment necessary for normative behavior (30); the findings thus support the importance of right prefrontal areas for normatively appropriate behaviors. Thus, a dysfunction of the right DLPFC, or its specific connections, may underlay certain psychopathological disorders that are characterized by excessive selfish tendencies and a failure to obey basic social norms. Fourth, the fact that there is no behavioral effect of right DLPFC disruption in the computer offer condition, where the reciprocity motive is absent, supports the role of the right DLPFC in the implementation of reciprocally fair behaviors. Fifth, the data show that only the right, but not the left, DLPFC activity plays a causal role, because disruption of the left DLPFC causes no behavioral changes relative to the sham control, whereas disruption of the right DLPFC sharply increases the acceptance rate of unfair offers. This fact is particularly interesting in the light of neuroimaging

data (9) that show that left DLPFC is activated if subjects face unfair offers, raising exciting questions about its exact role and the possible interplay of the left and the right hemispheres in the implementation of fairness-related behaviors that require an overriding of selfish impulses. Finally, the reported findings provide evidence for theoretical approaches (13–16) to social cognition and decision-making that stress the fundamental role of DLPFC in neural networks that support deliberative processes in human decision-making.

References and Notes

- R. T. Boyd, P. Richerson, *The Origin and Evolution of Cultures* (Oxford Univ. Press, Oxford, 2005).
- E. Fehr, U. Fischbacher, *Nature* **425**, 785 (2003).
- J. Henrich *et al.*, *Am. Econ. Rev.* **91**, 73 (2001).
- M. Rabin, *Am. Econ. Rev.* **83**, 1281 (1993).
- E. Fehr, K. M. Schmidt, *Q. J. Econ.* **114**, 817 (1999).
- W. Güth, R. Schmittberger, B. Schwarze, *J. Econ. Behav. Organ.* **3**, 367 (1982).
- C. F. Camerer, *Behavioral Game Theory—Experiments in Strategic Interaction* (Princeton Univ. Press, Princeton, NJ, 2003).
- L. A. Cameron, *Econ. Inq.* **37**, 47 (1999).
- A. G. Sanfey, J. K. Rilling, J. A. Aronson, L. E. Nystrom, J. D. Cohen, *Science* **300**, 1755 (2003).
- A. J. Calder, A. D. Lawrence, A. W. Young, *Nat. Rev. Neurosci.* **2**, 352 (2001).
- E. K. Miller, J. D. Cohen, *Annu. Rev. Neurosci.* **24**, 167 (2001).
- S. Freud, *The Ego and the Id* (Norton, New York, 1962).
- A. Bechara, *Nat. Neurosci.* **8**, 1458 (2005).
- A. B. Satpute, M. D. Lieberman, *Brain Res.* **1079**, 86 (2006).
- A. G. Sanfey, G. Loewenstein, S. M. McClure, J. D. Cohen, *Trends Cogn. Sci.* **10**, 108 (2006).
- G. F. Loewenstein, T. O'Donoghue, "Animal spirits: Affective and deliberative processes in economic behavior" (Social Science Research Network, 2004), available at SSRN <http://ssrn.com/abstract=539843>.
- Materials and methods are available as supporting material on *Science* Online.
- E. M. Robertson, H. Theoret, A. Pascual-Leone, *J. Cogn. Neurosci.* **15**, 948 (2003).

- B. Abler *et al.*, *Brain Topogr.* **17**, 193 (2005).
- M. van 't Wout, R. S. Kahn, A. G. Sanfey, A. Aleman, *Neuroreport* **16**, 1849 (2005).
- A. R. Aron, P. C. Fletcher, E. T. Bullmore, B. J. Sahakian, T. W. Robbins, *Nat. Neurosci.* **6**, 115 (2003).
- H. Garavan, T. J. Ross, E. A. Stein, *Proc. Natl. Acad. Sci. U.S.A.* **96**, 8301 (1999).
- A. R. Aron, T. W. Robbins, R. A. Poldrack, *Trends Cogn. Sci.* **8**, 170 (2004).
- D. Knoch *et al.*, *J. Neurosci.* **26**, 6469 (2006).
- S. E. Starkstein, R. G. Robinson, *J. Nerv. Ment. Dis.* **185**, 108 (1997).
- S. Blount, *Organ. Behav. Hum. Decis. Process.* **63**, 131 (1995).
- E. S. Barratt, M. S. Stanford, in *Personality Characteristics of the Personality Disorders*, C. G. Costello, Ed. (Wiley, New York, 1996), pp. 91–119.
- M. Perugini, M. Callucci, F. Presaghi, A. P. Ercolani, *Eur. J. Personality* **17**, 251 (2003).
- This study does not control for repeated measurements and finds no significant behavioral effect at the 5% level. This may be due to the fact that only seven subjects participated and that the two treatments (sham and the right DLPFC condition) were only 30 min apart.
- A. R. Damasio, *Descartes' Error: Emotion, Reason, and the Human Brain* (Harper Collins, New York, 1995).
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Supporting Online Material

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The Polarity Protein Par-3 Directly Interacts with p75^{NTR} to Regulate Myelination

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Cell polarity is critical in various cellular processes ranging from cell migration to asymmetric cell division and axon and dendrite specification. Similarly, myelination by Schwann cells is polarized, but the mechanisms involved remain unclear. Here, we show that the polarity protein Par-3 localizes asymmetrically in Schwann cells at the axon-glia junction and that disruption of Par-3 localization, by overexpression and knockdown, inhibits myelination. Additionally, we show that Par-3 directly associates and recruits the p75 neurotrophin receptor to the axon-glia junction, forming a complex necessary for myelination. Together, these results point to a critical role in the establishment of cell polarity for myelination.

The myelin sheath is a specialized membrane component in the vertebrate nervous system that is essential for the optimal transmission of neuronal action po-

entials. In the peripheral nervous system, Schwann cells (SC) are responsible for myelinating axons. Recently, environmental signals, particularly the neuregulins (1) and the neuro-

trophins (2, 3), have been shown to regulate SC myelination. Specifically, neurotrophin 3 (NT-3) promotes SC migration and inhibits myelination (2–4). In contrast, brain-derived neurotrophic factor (BDNF) inhibits SC migration and promotes myelination through the p75 neurotrophin receptor (NTR) (2, 3, 5). Much less is known, however, about the intrinsic mechanisms governing SC myelination. The formation of myelin by SCs is a highly polarized process, which consists of the unidirectional wrapping of multiple layers of membrane concentrically around an axon, initiated exclusively at the site of the axon-glia junction, raising the question of what regulates the asymmetric initiation of myelination.

To address this question, we examined the distribution of Par-3, a member of the Par family of adaptor proteins involved in the establishment of cell polarity in various cellular contexts (6–15) in SC/dorsal root ganglion (DRG) neuronal cocultures (Fig. 1A) and in sciatic nerves (Fig. 1B). Interestingly, we found that Par-3 is enriched asymmetrically at the membrane of