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You Shouldn't Have: Your Brain on Others' Crimes

Johannes Haushofer[1,*] and Ernst Fehr[1,*]
[1]Institute for Empirical Research in Economics, University of Zurich, Blumlisalpstrasse 10, 8006 Zurich
*Correspondence: johannes@iew.uzh.ch (J.H.), efehr@iew.uzh.ch (E.F.)
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Our legal system requires assigning responsibility for crimes and deciding on appropriate punishments. A new fMRI study by Buckholtz et al. in this issue of *Neuron* reveals that the right dorsolateral prefrontal cortex (rDLPFC) plays a key role in these cognitive processes. This finding sheds light on the neural mechanisms underlying moral judgment from a third-party perspective.

Much recent research documents people's willingness to punish norm violations and to enforce social norms. This willingness also exists if the punishers derive no material benefit themselves, but instead incur costs (Henrich et al., 2001). Even unaffected third parties who merely observe a norm violation engage in costly norm enforcement (Fehr and Fischbacher, 2004). Modern legal systems are probably based on these deep human instincts, aiming primarily at retribution: offenders are jailed or executed to *punish* them for their transgressions, and only in the second instance to prevent future harm to society (Kant, 1999; Whitman, 2003). Retributive punishment is thus a core element of contemporary justice. Judgment by third parties about punishment requires assigning responsibility for an offense that a perpetrator commits against a victim, judging the severity of that action, and finally selecting an appropriate punishment. Given the centrality of this process to the administration of justice, elucidating the cognitive and neural mechanisms underlying such judgments is of considerable interest.

In this issue of *Neuron*, Buckholtz and colleagues (Buckholtz et al., 2008) take a step in this direction: using functional magnetic resonance imaging (fMRI), they examine which brain regions are activated when humans make judgments regarding the appropriate punishments for various violations. Specifically, participants in their study read vignettes describing hypothetical transgressions that a fictitious agent, "John," commits against another person. The stories were divided into three conditions: in the first, the "responsibility" (R) condition, the perpetrator was responsible for the negative outcome of his action against the victim; in the "diminished responsibility" (DR) condition, mitigating circumstances were present that reduced the protagonist's responsibility; and finally, the "no crime" (NC) condition consisted of stories that did not describe crimes. The participants had to make judgments regarding the degree of punishment that the offender should receive, on a scale from 1 to 9.

The authors then proceeded to analyze the brain activation linked to these judgments. They contrasted activation in the "R" and "DR" conditions in order to identify neural correlates of responsibility. This contrast revealed a peak of activation in right doroslateral prefrontal cortex (rDLPFC). This activation did not simply reflect higher arousal resulting from reading the "R" compared to the "DR" stories, for two reasons: first, the stories were counterbalanced across subjects, so that the same stories appeared in the "R"

condition for one-half of subjects and the "DR" condition for the other half of subjects, with the only difference being the responsibility allocation. More importantly, the results in the rDLPFC remained the same when the two conditions were matched for reported arousal.

Interestingly, the same area in rDLPFC was activated in a second contrast between punished and nonpunished crimes from the "DR" condition. Thus, these findings suggest that rDLPFC might be involved in assigning responsibility for crimes or making judgments about appropriate punishments. However, rDLPFC did not exhibit a correlation between neural activation and punishment magnitude, suggesting that it does not directly underlie the decision on the amount of punishment. In contrast, there was some evidence that activation in amygdala and other emotion-related areas correlates with the degree of punishment subjects assign to the protagonist: higher punishment scores were associated with higher activation in these regions during the decision period.

These findings complement a number of previous studies and shed new light on the role of right DLPFC in judgments involving the normative dimensions of social interactions. This region has previously been highlighted in a number of studies addressing questions similar to those studied by Buckholtz et al.: an early study (Sanfey et al., 2003) found increased activation in rDLPFC when subjects were involved in fairness judgments and decided whether to reject a low offer in an ultimatum game, compared to when they received a high offer. However, as in Buckholtz et al., the punishment decision was not correlated with activity in right DLPFC, i.e., subjects with higher DLPFC activation punished neither more nor less than those with less DLPFC activation. The work of Greene et al. (2004) suggests that this brain region is involved in normative evaluations involving conflicting moral goals. They presented participants with moral scenarios similar to the famous trolley dilemma (Thomson, 1976) and compared trials in which subjects acted in the interest of greater aggregate welfare (utilitarian decisions) at the expense of personal moral standards (e.g., killing one's child to keep its crying from raising the attention of enemy soldiers). Again this contrast showed activation in rDLPFC. The same region was also found to be active in another study by Spitzer et al. (2007) involving social decision making: these authors scanned the first mover in a game similar to the ultimatum game, where this person can choose to transfer any amount of her endowment to another player, who then can punish the first mover for unfair transfer levels. The study found that rDLPFC was more active when the first player was threatened with punishment for making small transfers to the second player compared to a control treatment in which punishment was not an option. The punishment threat thus activates the rDLPFC in the player who faces the threat. Moreover, the activation in rDLPFC was the stronger the more subjects changed their behavior in the ultimatum game (when they faced the punishment threat) relative to the control treatment (when they did not face a threat). Finally, deactivating the rDLPFC with repetitive transcranial magnetic stimulation (TMS) reduced participants' ability to reject unfair offers in the ultimatum game, although participants' ability to judge these offers as unfair was not impaired (Knoch et al., 2006).

How does the new study fit together with the previous ones? To what extent is it possible to provide a unifying interpretation of the role of rDLPFC across all of these studies? The findings described above are all consistent with for the notion that rDLPFC is involved in inhibiting prepotent responses: rejecting a low ultimatum game offer (Sanfey et al., 2003) means losing money and thus requires overriding the impulse to accept the money; making utilitarian rather than emotion-driven moral decisions (Greene et al., 2004) and resisting the impulse to make low transfers (Spitzer et al., 2007) also require the suppression of knee-jerk responses. The activation of rDLPFC in these studies is consistent with the view that rDLPFC is involved in overriding such responses. In addition, the TMS study (Knoch et al., 2006) mentioned above even suggests a key *causal* role of rDLPFC for overriding prepotent impulses because if rTMS inhibits the recruitment of rDLPFC, subjects are less able to resist the temptation to accept unfair money offers.

Is the new study by Buckholtz and colleagues consistent with this view of the role of rDLPFC? The crucial new element of this study is the fact that participants were instructed to determine "appropriate" judgments of punishment from a *third-person perspective*. Thus, participants acted like criminal judges; the fact that their punishment decisions correlated strongly with the prison sentences they deemed appropriate for the crimes in question attests to the fact that they saw themselves in this role. Inasmuch as judges are expected to act impartially and objectively, this task, too, requires the suppression of prepotent responses to the crimes described, to produce "just" and impartial punishments. Reading stories about severe crimes may well cause arousing emotional responses that may be associated with a strong desire to punish. Buckholtz et al. report, in fact, that right amygdala is strongly positively correlated with punishment judgments—a finding consistent with the role of this brain region in the representation of arousing emotional events. However, the demands of impartiality often require overriding these impulses in order to produce a reasonable judgment. The higher activation of rDLPFC in the R compared to the DR condition and during punished versus nonpunished trials is therefore consistent with a role for rDLPFC in the suppression of prepotent emotional reactions.

Thus, the study of Buckholtz makes a valuable contribution in that it illustrates that third-person judgment situations, such as those used in their study, may rely on similar neural mechanisms as two-person economic and social exchanges. While it is difficult to draw reverse inferences about mental states based on brain activation (Poldrack, 2006), one might speculate, based on this new study, that the mental processes motivating judicial verdicts involve the suppression of prepotent emotional reactions in favor of impartial and objective verdicts. Thus, this new result might, if confirmed by future studies, elucidate the neural source of judicial impartiality.

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PirB, a Second Receptor for the Myelin Inhibitors of Axonal Regeneration Nogo66, MAG, and OMgp: Implications for Regeneration In Vivo

Marie T. Filbin[1,*]
[1]Biology Department, Hunter College, 695 Park Avenue, New York, NY 10065, USA
*Correspondence: filbin@genectr.hunter.cuny.edu
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Inhibitors of axonal regeneration in myelin are believed to be major contributors to the lack of regeneration in the adult CNS. Three of the four known myelin inhibitors, although very different structurally, interact with the same receptor, NgR. However, the absence of NgR has no effect on inhibition of neurite outgrowth in culture, and there is no improvement in CST regeneration in vivo. In a recent issue of *Science*, a second receptor for these myelin inhibitors was described, PirB, a receptor first described in the immune system. Will PirB be the answer to CST regeneration in vivo?

In the early 1990s, a monoclonal antibody, termed IN-1, was believed to be the solution to axonal regeneration in the adult mammalian spinal cord (Caroni and Schwab, 1988). At the time, the precise identity of the IN-1 antigen was unknown; however, it was known to be a component of the myelin membrane, thought to be one of the major obstacles to spontaneous axonal regeneration after injury. In culture the IN-1 antibody allowed neurons to extend long processes; when grown in the inhibitory environment of myelin and in vivo, it promoted axonal regeneration (Caroni and Schwab, 1988; Schnell and Schwab, 1990). The next steps, then, appeared simple—identify the IN-1 antigen and its receptor, and the molecular lock to promoting spinal axon regeneration would be opened.

Alas, as with most biological problems, the answer was not so simple. Even before the IN-1 antigen had been cloned, another potent regeneration inhibitor was identified in myelin, the myelin-associated glycoprotein (MAG) (McKerracher et al., 1994; Mukhopadhyay et al., 1994). The subsequent identification of the IN-1 antigen (which may be one of many, but the only one identified to date) as a protein termed NogoA, revealed that the protein carried two inhibitory domains, only one of which, within the amino terminus, termed Amino-Nogo, was recognized by the IN-1 antibody; the second inhibitory domain, carried by a string of 66 amino acids, was termed Nogo66 (GrandPre et al., 2000; Huber and Schwab, 2000; Prinjha et al., 2000). Later, a third myelin protein, the oligodendrocyte-myelin glycoprotein (OMgp) was also shown to be inhibitory for neurite outgrowth (Wang et al., 2002). So now there were four inhibitors (two on NogoA) identified in myelin. As these inhibitors shared no sequence or even domain similarity with each other, it was presumed they would each have their own receptor. It came as a real surprise, then, that the binding partner identified for Nogo66, termed Nogo receptor (NgR), was also shown to bind MAG and OMgp (Domeniconi et al., 2002; Fournier et al., 2001; Wang et al., 2002). So, again, a somewhat simple answer to axonal regeneration in vivo presented itself; namely, if this single receptor could be neutralized or eliminated in vivo, then the effects of three of the four major inhibitors in myelin would be lost, and regeneration should proceed.

Not so. Two groups reported studies in which NgR had been knocked out. One study, from the Strittmatter group, reported a loss of the growth cone collapse response to the myelin inhibitors and limited regeneration of the raphespinal and rubrospinal tracts, but no regeneration of the corticospinal tract (CST) (Kim et al., 2004; Zheng et al., 2005). A second study, by the Tessier-Lavigne group,