

## NEUROSCIENCE

## Brain stimulation reveals crucial role of overcoming self-centeredness in self-control

Alexander Soutschek,<sup>1\*</sup> Christian C. Ruff,<sup>1</sup> Tina Strombach,<sup>2</sup> Tobias Kalenscher,<sup>3</sup> Philippe N. Tobler<sup>1</sup>

2016 © The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. Distributed under a Creative Commons Attribution NonCommercial License 4.0 (CC BY-NC).

Neurobiological models of self-control predominantly focus on the role of prefrontal brain mechanisms involved in emotion regulation and impulse control. We provide evidence for an entirely different neural mechanism that promotes self-control by overcoming bias for the present self, a mechanism previously thought to be mainly important for interpersonal decision-making. In two separate studies, we show that disruptive transcranial magnetic stimulation (TMS) of the temporo-parietal junction—a brain region involved in overcoming one's self-centered perspective—increases the discounting of delayed and prosocial rewards. This effect of TMS on temporal and social discounting is accompanied by deficits in perspective-taking and does not reflect altered spatial reorienting and number recognition. Our findings substantiate a fundamental commonality between the domains of self-control and social decision-making and highlight a novel aspect of the neurocognitive processes involved in self-control.

## INTRODUCTION

The ability to exert self-control is key to human success and well-being (1, 2). Self-control refers to the capacity to choose valuable long-term goals (for example, health or saving for the future) over immediate temptations (3). The standard account of self-control assumes that choosing delayed rewards requires impulse control processes that dampen the desire to select the immediately rewarding option (4). Therefore, neural models of delay discounting mainly focus on the lateral prefrontal cortex, which is thought to play a key role in resisting temptations through impulse control (5, 6). Here, we provide evidence for a different self-control mechanism that promotes choices of delayed rewards by allowing a focus on the perspective of one's future needs, a process that is neurally implemented by the temporo-parietal junction (TPJ).

At first glance, TPJ involvement in delaying gratification may appear counterintuitive, because the TPJ has been associated with other cognitive functions (7–12), particularly social cognition (13). Prosocial behavior requires overcoming one's own perspective, a mechanism thought to be neurally implemented in the posterior TPJ (pTPJ) (8, 10). Thus, on further reflection, an involvement of the pTPJ in delay of gratification is actually plausible: Delaying gratification requires taking the perspective of one's future self (14), which humans may approach like a complete stranger according to philosophical accounts (15). We therefore hypothesize that intertemporal decision-making, although typically considered to be distinct from interpersonal decision-making (16), relies on a neural mechanism implemented in the pTPJ that overcomes the bias of the (present) self.

We tested the functional role of the pTPJ in delay of gratification with transcranial magnetic stimulation (TMS) in two independent studies. Study 1 provided evidence for a causal involvement of the identical pTPJ subregion in both patient and prosocial behavior. Subjects performed an intertemporal decision task and an interpersonal decision task after TMS had been used to temporally disrupt either the right pTPJ or the vertex as a control site. In the intertemporal decision task (Fig. 1A), subjects chose between an immediate smaller reward and a delayed larger reward. In the interpersonal decision task (Fig. 1B), subjects chose

between a selfish reward option and a prosocial reward option in which an amount of money was split between themselves and a second person (9, 16–18). The social distance of the second person was manipulated parametrically from very close persons (low social distance) to strangers (high social distance). On the basis of the common neural mechanism assumption, we hypothesized that disrupting pTPJ functioning biases individuals toward both more selfish and more impulsive choices.

The goals of Study 2 were to replicate the results of Study 1 and to determine the cognitive mechanisms underlying the effects of TMS over the pTPJ. Choosing a delayed or a prosocial reward involves one's self-centered bias (14, 19), because the ability to dissociate from one's current state is thought to constitute a crucial and common determinant of social cognition and future thinking (20). This notion is supported by clinical studies showing that autistic children suffer not only from deficits in theory of mind and mentalizing (21) but also from impaired future thinking (22). Therefore, we reasoned that the pTPJ promotes delay of gratification by implementing processes required for overcoming the bias of the present self. If this hypothesis is true, then the same pTPJ subregion involved in intertemporal decision-making should have a causal role in overcoming egocentricity bias too. To test this prediction, subjects also performed a perspective-taking task that required them to resolve conflicts between their own and other's perspectives in addition to the intertemporal and interpersonal decision tasks in Study 2.

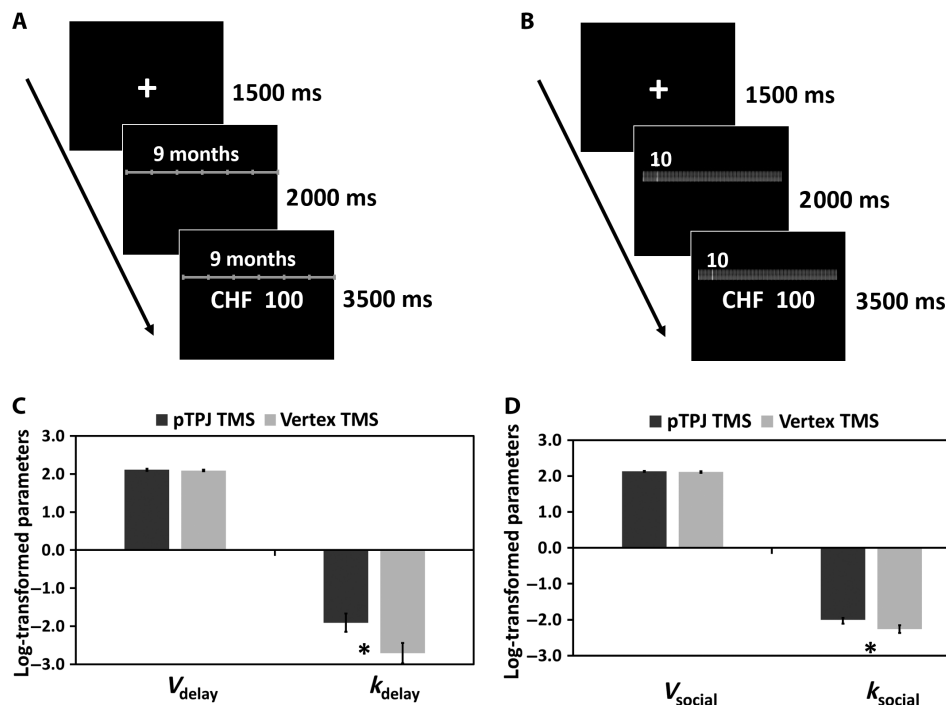
## RESULTS

**pTPJ promotes delay of gratification and prosocial behavior**

To test the hypothesis that the pTPJ plays a crucial role in delaying gratification, subjects performed an intertemporal decision task and an interpersonal decision task after we administered an inhibitory form of TMS over the pTPJ or vertex (between-subject design). We used a continuous theta-burst stimulation (cTBS) protocol (23) to temporally disrupt either the right pTPJ or the vertex to control for site-unspecific stimulation effects (24). In the intertemporal decision task, subjects chose between a variable reward (0 to 160 Swiss francs) given immediately and a fixed reward (160 Swiss francs) received after a delay of 3 to 18 months. In the interpersonal decision task, subjects made choices between a selfish reward only for themselves (75 to 155 Swiss francs) and a prosocial reward that was equally shared between themselves and a person at varying social distances (75 Swiss francs for subject and other).

<sup>1</sup>Laboratory for Social and Neural Systems Research, Department of Economics, University of Zurich, Zurich, Switzerland. <sup>2</sup>Department of Economics, Heinrich Heine University, Düsseldorf, Germany. <sup>3</sup>Department of Psychology, Heinrich Heine University, Düsseldorf, Germany.

\*Corresponding author. Email: alexander.soutschek@econ.uzh.ch



**Fig. 1. Tasks and stimulation effects in Study 1.** Illustration of trial structure for (A) the intertemporal decision task and (B) the interpersonal decision task. In the intertemporal decision task, we presented first the temporal delay information (3 to 18 months), followed by the immediate reward (0 to 160 Swiss francs); the delayed reward was fixed to 160 Swiss francs). Likewise, we presented first the social distance information (0 to 100) and then the selfish reward (75 to 155 Swiss francs) in the interpersonal decision task. The prosocial reward was fixed to 75 Swiss francs for the subject and the other person. (C and D) Log-transformed parameter estimates ( $\pm$ SEM) for the intercepts  $V_{\text{delay/social}}$  and the discount factors  $k_{\text{delay/social}}$  in (C) the intertemporal decision task and (D) the interpersonal decision task. \* $P < 0.05$ .

To analyze task performance, we first determined for each subject the individual indifference values for each delay in the intertemporal decision task, and for each social distance in the interpersonal decision task (see Materials and Methods for details). As expected, for both tasks and in both TMS conditions, indifference values decreased as (temporal or social) distance increased. We then fitted hyperbolic functions to all the indifference values in each subject, separately for the intertemporal and interpersonal decision tasks (16, 17), and separately for the pTPJ TMS and the vertex TMS groups (fig. S1). The shape of the discount functions is determined by two parameters: the intercepts  $V_{\text{delay}}$  or  $V_{\text{social}}$  and the discount factors  $k_{\text{delay}}$  or  $k_{\text{social}}$  (steepness of the curve). Whereas  $V_{\text{delay}}$  and  $V_{\text{social}}$  can be interpreted as the willingness to wait for delayed rewards and to share money with others at minimal delays and social distances, respectively,  $k_{\text{delay}}$  and  $k_{\text{social}}$  measure the discounting of delayed/shared rewards with increasing temporal delay/social distance. Thus, estimating both the intercepts and the slopes of the hyperbolic functions allowed us to disentangle potential TMS effects on the subjects' impulsivity/prosociality at minimal delays/social distances from the discounting of delayed/shared rewards with increasing delays/social distances. We also used a one-parameter model, fixing the intercept and leaving only  $k_{\text{delay}}$  and  $k_{\text{social}}$  free, to fit the indifference values. The two-parameter model showed considerably better model fits than the one-parameter model did even when considering the number of free parameters in the models (see Supplementary Results). This suggests that the model with free intercepts provided a better explanation for the observed data.

Our common neural mechanism assumption leads to the hypothesis that disrupting pTPJ functioning should steepen the discounting of both delayed and prosocial rewards. That is, we predict TMS over the

pTPJ to result in a stronger decline of the subjective value of delayed and prosocial rewards with increasing temporal delay or social distance, respectively. To statistically assess the difference between groups, we analyzed the effects of TMS on the log-transformed parameters  $V_{\text{delay}}$  and  $V_{\text{social}}$  as well as  $k_{\text{delay}}$  and  $k_{\text{social}}$  with a mixed-measures analysis of variance (ANOVA) including the between-subject factor TMS (pTPJ TMS versus vertex TMS) and the within-subject factors Task (intertemporal versus interpersonal decision task) and Parameter ( $V_{\text{delay}}$  versus  $k_{\text{delay}}$  and  $V_{\text{social}}$  versus  $k_{\text{social}}$ ). Besides a significant main effect of Parameter ( $F_{1,41} = 1983.22$ ,  $P < 0.001$ , partial  $\eta^2 = 0.980$ ), the ANOVA revealed a significant TMS  $\times$  Parameter interaction ( $F_{1,41} = 6.96$ ,  $P < 0.05$ , partial  $\eta^2 = 0.145$ ), suggesting that TMS had dissociable effects on the intercepts  $V_{\text{delay}}/V_{\text{social}}$  and the discount parameters  $k_{\text{delay}}/k_{\text{social}}$ . No further effect passed the statistical threshold.

Given the significant TMS  $\times$  Parameter interaction, we examined in more detail how TMS affected the estimated parameters by computing separate ANOVAs for the intertemporal and the interpersonal decision tasks. We first tested TMS effects on temporal discounting with a 2 (TMS)  $\times$  2 (Parameter) mixed-measures ANOVA on the log-transformed parameters  $k_{\text{delay}}$  and  $V_{\text{delay}}$  in the intertemporal decision task (Fig. 1C). We found a significant TMS  $\times$  Parameter interaction ( $F_{1,41} = 4.79$ ,  $P < 0.05$ , partial  $\eta^2 = 0.105$ ), suggesting that pTPJ TMS, relative to vertex TMS, increased the discount parameter  $k_{\text{delay}}$  ( $t_{41} = 2.24$ ,  $P < 0.05$ ), whereas we found no TMS effects on the intercept  $V_{\text{delay}}$  ( $t_{41} < 1$ ,  $P = 0.53$ ). Thus, pTPJ TMS resulted in steeper delay discounting as delay to reward increased but left the processing of delayed rewards at minimal delays relatively unchanged. This supports the notion of a crucial role of the pTPJ in implementing self-control.

We then assessed how pTPJ TMS affects social discounting by computing the same mixed-measures ANOVA, but now predicting the

parameters  $V_{\text{social}}$  and  $k_{\text{social}}$  in the interpersonal decision task (Fig. 1D). We found a significant TMS  $\times$  Parameter interaction ( $F_{1,41} = 4.18$ ,  $P < 0.05$ , partial  $\eta^2 = 0.093$ ): The discount parameter  $k_{\text{social}}$  was also significantly increased following pTPJ TMS compared with vertex TMS ( $t_{41} = 2.14$ ,  $P < 0.05$ ), whereas the undiscounted self-reward value  $V_{\text{social}}$  did not differ between TMS groups ( $t_{41} = 1.07$ ,  $P = 0.29$ ). Thus, similar to temporal discounting, TMS over the pTPJ resulted in steeper discounting of more distant rewards as distance increased and left undiscounted reward value processing relatively unchanged. Together, these results indicate that the pTPJ plays a causal role in rendering behavior both future-oriented and prosocial.

The results of Study 1 support our conjecture that the pTPJ implements a common mechanism in intertemporal and interpersonal decision-making that may be related to overcoming the bias for the present self. This notion leads to two strong predictions: First, the stimulated pTPJ subregion should be involved not only in temporal and social discounting but also in overcoming egocentricity bias in situations that require taking the perspective of a stranger. Second, individual differences in the ability to overcome egocentricity bias should predict the steepness of social and temporal discounting. To test these predictions, we conducted a second study in which we could replicate the results of Study 1 while also measuring perspective-taking in a separate task (25). In this Study 2, we also controlled for potential confounding effects of pTPJ TMS on spatial reorienting of attention and on number recognition. These processes have previously been related to TPJ activation (12, 26), and they might, in principle, play a role in our experimental tasks. Because there was no evidence for TMS effects on these control measures, the impact of pTPJ TMS on temporal and social discounting cannot be explained by a potential pTPJ involvement in attentional reorienting or number cognition (see Supplementary Results). Finally, to more extensively control for site-unspecific TMS effects, we also collected data from an active TMS control site [applying TMS over the primary somatosensory cortex (S1)] in addition to TMS over the pTPJ and vertex.

### Effects of pTPJ TMS on temporal and social discounting replicate

First, we analyzed the effects of pTPJ TMS on temporal and social discounting in the replication experiment. In contrast to Study 1, we presented the social distance/temporal delay in a vertical fashion, on either the left or the right side of the screen, with the selfish/immediate options presented on the opposite side (counterbalanced across subjects; Fig. 2, A and B). We again fitted hyperbolic functions to the individual indifference values in the intertemporal and interpersonal decision tasks (fig. S2). Next, we computed a mixed-measures ANOVA testing the effects of TMS (pTPJ TMS versus S1 TMS versus vertex TMS), Task, and Parameter on the log-transformed parameters  $V_{\text{delay}}$  and  $V_{\text{social}}$  as well as  $k_{\text{delay}}$  and  $k_{\text{social}}$ , as estimated in the hyperbolic temporal and social discounting functions of the replication experiment (Fig. 2, C and D). As in Study 1, we found a significant main effect of Parameter ( $F_{1,56} = 4006.28$ ,  $P < 0.001$ , partial  $\eta^2 = 0.986$ ), which was modulated by a Parameter  $\times$  Task interaction ( $F_{1,56} = 6.36$ ,  $P < 0.05$ , partial  $\eta^2 = 0.101$ ). We also replicated the finding of a TMS  $\times$  Parameter interaction ( $F_{2,56} = 3.50$ ,  $P < 0.05$ , partial  $\eta^2 = 0.111$ ), again suggesting differential effects of TMS on  $k_{\text{delay}}$  and  $k_{\text{social}}$  versus  $V_{\text{delay}}$  and  $V_{\text{social}}$ . As hypothesized, post hoc tests revealed that pTPJ TMS, relative to both vertex TMS and S1 TMS, led to higher discount factors  $k_{\text{delay}}$  and  $k_{\text{social}}$  for temporal discounting and social discounting (all  $t > 1.70$ , all  $P < 0.05$ ), whereas we found no TMS effect on the intercepts  $V_{\text{delay}}$  and  $V_{\text{social}}$

(all  $t < 1.23$ , all  $P > 0.24$ ). There were no significant differences between the control groups S1 TMS and vertex TMS (all  $t < 1.51$ , all  $P > 0.14$ ). This replicates our findings of Study 1 and confirms that disrupting pTPJ functioning leads to steeper discounting of delayed and prosocial rewards. Moreover, variations in the task design of Study 2 and control experiments showed that the stimulated TPJ region is not related to attentional reorienting or number line processing (see Supplementary Results).

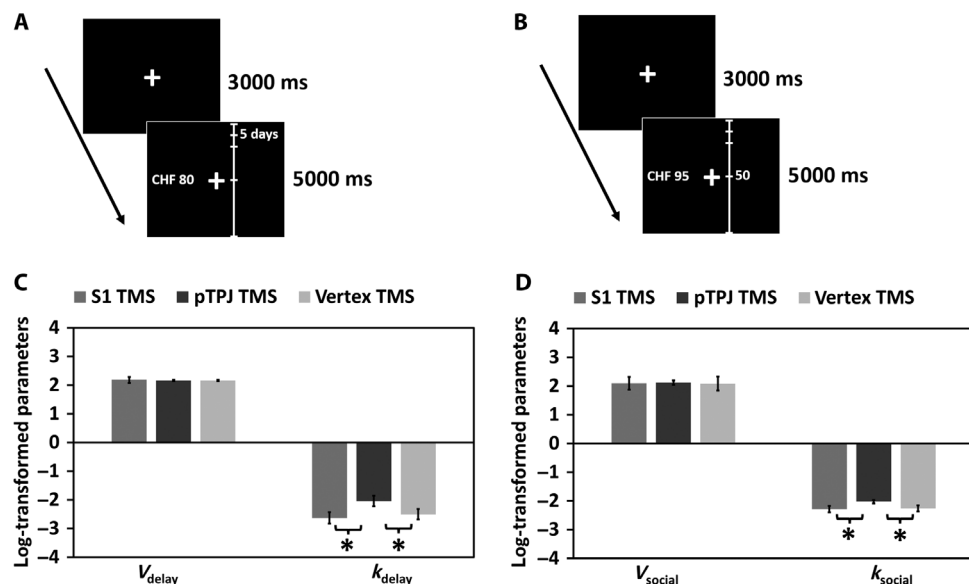
### pTPJ contributes to overcoming egocentricity bias

We hypothesized that the pTPJ promotes patient and prosocial choices by suppressing egocentricity bias (9). To test this hypothesis, we examined TMS effects on performance in a well-established perspective-taking task in which we displayed an image of a room showing 0 to 3 red discs at the left and/or the right wall of the room (25). An avatar facing either the left or the right wall could see only the discs at the wall it was facing, whereas subjects could see the discs on both walls (Fig. 3A). Thus, the subjects and the avatar could see either the same (congruent perspectives) or different numbers of discs (incongruent perspectives). The task was to determine the number of discs seen either from the perspective of the subject (self-perspective) or from the perspective of the avatar (other-perspective). A stronger egocentricity bias is indicated by lower performance when judging incongruent relative to congruent perspectives from the perspective of the avatar relative to one's own perspective (25). We analyzed how TMS changed this egocentricity bias by comparing performance before and after the TMS intervention. We analyzed error rate differences (post-TMS – pre-TMS) using a mixed-measures ANOVA including the factors TMS (pTPJ versus S1 versus vertex), Perspective (self versus other), and Incongruence (congruent versus incongruent). The analysis revealed a significant main effect of Incongruence ( $F_{1,56} = 5.08$ ,  $P < 0.05$ , partial  $\eta^2 = 0.083$ ), which was qualified by a significant TMS  $\times$  Perspective  $\times$  Incongruence interaction ( $F_{2,56} = 3.61$ ,  $P < 0.05$ , partial  $\eta^2 = 0.114$ ). This finding suggests that the effects of TMS on resolving conflicts between self- and other-perspective are dependent on the stimulation site and the given perspective (Fig. 3B).

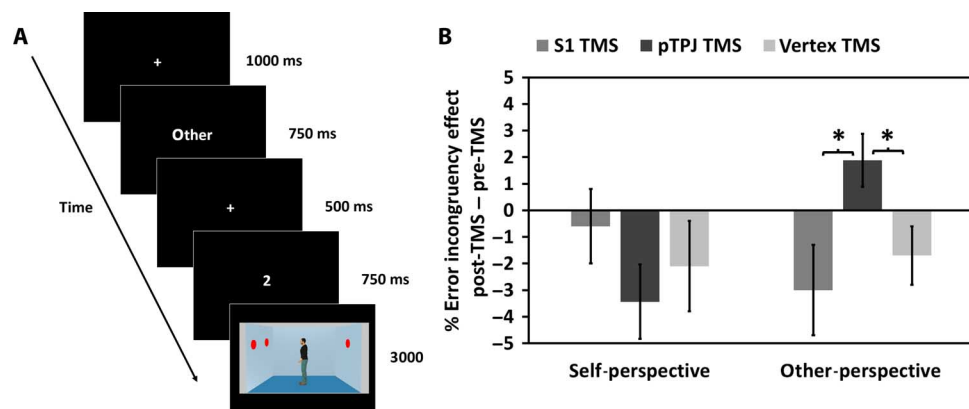
Next, we computed incongruence effects separately for the self- and other-condition by subtracting error rates on congruent trials from those on incongruent trials. These incongruence effects reflect performance costs when the subject's and the avatar's perspectives were incompatible (that is, they saw different numbers of discs) compared to when their perspectives were compatible (that is, both saw the same number of discs). Then, we tested whether the magnitude of these incongruence effects can be predicted by the factor TMS by computing separate  $t$  tests for the self-perspective and the other-perspective. As expected, pTPJ TMS resulted in significantly larger incongruence effects than both S1 and vertex TMS in the other-perspective condition (all  $t > 2.39$ , all  $P < 0.05$ ). By contrast, pTPJ TMS had no effect in the self-perspective condition (all  $t < 1.15$ , all  $P > 0.26$ ) (note that negative incongruence effect differences between post- and pre-TMS reflect practice-induced performance improvements, which are prevented by pTPJ TMS on other-perspective trials). There were no significant differences between the S1 TMS and vertex TMS groups (all  $t < 1$ , all  $P > 0.54$ ). This confirms our hypothesis that the stimulated TPJ subregion has a causal role in overcoming egocentricity bias.

### Egocentricity bias predicts impulsive and selfish behavior

To substantiate the hypothesis that overcoming egocentricity constitutes a common mechanism underlying temporal and social discounting,



**Fig. 2. Tasks and stimulation effects in Study 2.** Trial structure for (A) the intertemporal decision task and (B) the interpersonal decision task. Temporal delay (1 to 180 days)/social distance (0 to 100) information was presented simultaneously with the immediate/selfish reward. (C and D) Log-transformed parameter estimates ( $\pm$ SEM) for the intercepts  $V_{\text{delay/social}}$  and the discount factors  $k_{\text{delay/social}}$  in (C) the intertemporal decision task and (D) the interpersonal decision task. \* $P < 0.05$ .



**Fig. 3. Perspective-taking task and stimulation effects.** (A) Trial structure. Subjects indicated whether the number of red discs seen from their own perspective (self) or from the perspective of the avatar (other) matched the number indicated by a cue. The avatar could see only the discs on the wall it was facing, whereas subjects could see the discs on both walls. Therefore, the perspectives of the subject and of the avatar were either congruent (the subject and the avatar saw the same number of discs) or incongruent (the subject and the avatar saw a different number of discs). (B) Error incongruency effects (incongruent-congruent perspectives). Compared to control TMS (S1 and vertex TMS), TMS of pTPJ reduced performance when subjects had to judge the number of discs from the perspective of the avatar but not when they judged from their own perspective. Error bars reflect  $\pm 1$  SEM. \* $P < 0.05$ .

we tested whether individual differences in the ability to overcome egocentricity predict the degree of temporal and social discounting. On the basis of the three-way TMS  $\times$  Perspective  $\times$  Incongruence interaction reported above, we quantified egocentricity bias by calculating for each individual the difference in the number of errors between the other-perspective and the self-perspective conditions at pre-TMS. This was done to obtain a measure of egocentricity bias unaffected by TMS effects. We then used this measure to predict the log-transformed discount rates in the intertemporal and interpersonal decision tasks, controlling for TMS effects on discount rates. If temporal and social discounting require shifting the perspective from the current self to the future self or to others, respectively, then a stronger egocentricity bias should predict more impulsive and more selfish choices. In line with our hypothesis, egocentricity bias in the perspective-taking task pre-

dicted discount rates in the intertemporal decision task ( $r_{55} = 0.30$ ,  $P < 0.05$ ) and the interpersonal decision task ( $r_{55} = 0.42$ ,  $P < 0.01$ ). Thus, a strong egocentricity bias (that is, high incongruence effect differences between other- and self-perspective) predicted more impulsive and more selfish choices. This supports the notion that both intertemporal and interpersonal decision-making draw upon the capability to resolve conflicts between different perspectives.

### DISCUSSION

Our findings provide evidence for a novel neural self-control mechanism implemented by the pTPJ that promotes patient choices by overcoming egocentricity bias. Whereas the main focus of research on intertemporal decision-making has been on how self-control processes

localized in the lateral prefrontal cortex implement long-term goals (5, 6, 27), our findings show that the pTPJ also has a role in implementing future-oriented behavior. In analogy to overcoming egocentricity bias in social discounting, the pTPJ may resolve conflicts between present- and future-oriented motives by shifting attention away from the perspective of the current self. This is in line with studies suggesting that intertemporal decision-making requires taking the perspective of the future self (14, 28), a process related to pTPJ activation (29). Thus, it appears that patient choices can be promoted by at least two distinct mechanisms, which are related to dissociable neural networks: First, self-control processes implemented in the lateral prefrontal cortex may override the temptation to select the immediate reward (5, 6). Current theories posit the lateral prefrontal cortex to encode higher-order goals such as maximizing one's monetary payoff and to bias patient choices by increasing the weight of these goals in neural reward circuits (27, 30). Second, overcoming egocentricity bias implemented in the pTPJ may enhance the value of future rewards by a change in perspective away from one's current self.

Our data speak against the possibility that TMS of the currently stimulated pTPJ region affected attentional reorienting (see Supplementary Results). Similarly, our findings provide no evidence for pTPJ involvement in number processing. Note, however, that the demands of the number line task (mapping an alphanumeric number on a visual scale) differed somewhat from the number processing requirements in the choice tasks (in which delays and social distances were indicated not only by visual scales but also by numbers). Therefore, future studies may want to more carefully consider a potential pTPJ involvement in number processing. However, note that, typically, the inferior parietal cortex rather than the pTPJ has been related to number processing (26).

On the basis of the observed pTPJ involvement in perspective-taking, we propose that the pTPJ promotes delay of gratification by strengthening the focus on one's future needs. Theoretically, the pTPJ might also facilitate self-control by reducing sensitivity to the immediate option (30), rather than by increasing the value of delayed rewards. However, if this was the case, one would expect to find effects of pTPJ TMS on the intercept  $V$ , which corresponds closely to the value of immediate rewards. Because we found specific pTPJ TMS effects on the discount parameter  $k$ , but not  $V$ , it seems unlikely that the pTPJ is involved in encoding the value of immediate rewards. Instead, our results suggest the pTPJ plays a crucial role in the discounting of delayed rewards by temporal delay.

According to dual-system accounts of intertemporal choice (4, 6, 31), temporal discounting results from competition between an impulsive  $\beta$ -system (which is sensitive to immediate rewards) and a patient  $\delta$ -system (which favors long-term goals). Because our results suggest the pTPJ plays a crucial role in increasing the weight of delayed rewards, the pTPJ may relate to the patient  $\delta$ -system in the terminology of dual-system accounts. In line with this hypothesis, pTPJ TMS preferentially affected the  $\delta$  parameter but not  $\beta$  (Supplementary Results). Within this framework, the pTPJ would relate to the patient  $\delta$ -system rather than the impulsive  $\beta$ -system. However, in the literature, the  $\delta$ -system is thought to involve rationality and higher-order deliberative processes rather than overcoming egocentricity (6). Thus, our perspective-taking results reveal potential avenues for reinterpreting or extending dual-system models of temporal discounting.

Our findings imply that the pTPJ may be a promising novel target for impulsivity-related health interventions. Individuals with substance addiction, for example, show steeper temporal discounting than healthy

controls (32, 33). Because this is often interpreted as indicating impulse control deficits, translational research on pathological self-control deficits predominantly focuses on frontostriatal circuits (34). Our data support the complementary view that addiction may also reflect a stronger bias toward the perspective of the present self (35) and suggest two potentially dissociable neural phenotypes of addiction or other self-control-related disorders. In addition, the assumption of a common neural mechanism involved in interpersonal and intertemporal decision-making makes the strong prediction that disorders related to self-control problems may go hand in hand with deficits in social decision-making (36).

## MATERIALS AND METHODS

### Study 1

#### Participants.

Forty-three volunteers (19 female, 24 male;  $M_{\text{age}} = 23.1$ ,  $SD_{\text{age}} = 2.3$ ) were recruited at the University of Zurich to participate in the study. The study protocol was approved by the Research Ethics Committee of the canton of Zurich. All subjects gave written informed consent. For their participation, they were paid CHF 40/hour and a monetary bonus depending on their choices (see below). The investigation was conducted in full accordance with the principles expressed in the Declaration of Helsinki.

#### Task design.

Subjects performed two tasks: one requiring them to make intertemporal decisions, and the other involving interpersonal decisions. In the intertemporal decision task, subjects had to choose between a smaller immediate reward and a larger later reward, where the immediate reward ranged from 0 to 160 Swiss francs in steps of 20, resulting in nine immediate reward levels. The larger later reward was held constant at 160 Swiss francs, with the temporal delay varying from 3 to 18 months in steps of 3 months. Temporal delay was indicated by a visual scale ranging from 0 to 18 months. Subjects gave their responses by pressing the left or the right control key with the left or the right index finger, respectively, on a QWERTZ keyboard. The assignment of left/right button presses to choices of the immediate and the delayed reward was counterbalanced across subjects.

In the interpersonal decision task (9, 17), we asked subjects to imagine a list of 100 people ranging from 1 (the person socially closest to them) to 100 (a random stranger on the street). A person at rank 50 was described as a person that the subject had seen several times without knowing their name. Subjects were discouraged to think of people that they felt negatively toward. In the computer experiment, we used only the social distances of 1, 5, 10, 20, 50, and 100. The social distance was indicated using a visual scale that consisted of 101 icons, representing the subject (icon 1) and her social world on the social distance scale. One icon was highlighted and indicated the social distance of the recipient in the current trial. The task was to choose between a selfish option, in which only the subject obtained a reward, and a prosocial option, in which a reward was shared equally (75 Swiss francs for each) between the subject and a person indicated on the social distance scale. In different trials, nine selfish reward amounts were used, ranging from 75 to 155 Swiss francs in steps of 10. Again, subjects pressed the left and the right control keys to indicate their decisions for the selfish or prosocial reward option, with the assignment of response keys to choices counterbalanced across subjects.

**Procedure.**

Before performing the experimental tasks, subjects were stimulated with TMS (see below). Then, subjects performed one block of the intertemporal decision task and one block of the interpersonal decision task (block order was counterbalanced across participants). Each block contained a total of 54 trials, such that every combination of temporal delays and immediate rewards in the intertemporal decision task as well as every combination of social distances and selfish rewards in the interpersonal decision task was presented once during the experiment. Trials were presented in randomized order.

The trial structure was identical for both tasks (Fig. 1): Each trial started with the presentation of a central fixation cross (1.5 s), followed by a visual scale indicating the temporal delay or the social distance (2 s). Finally, the amount of the immediate or selfish reward option was displayed for 3.5 s. During this last phase of every trial, subjects indicated their choices via key press. Note that the amount of the delayed or the prosocial reward option was not presented because these values remained constant throughout the task.

At the end of the experiment, a single trial of each task was randomly selected and implemented. For both tasks, if subjects chose the immediate or the selfish option in the selected trial, they received  $1/10$  of the corresponding amount immediately and in addition to their basic payment (9). In the intertemporal decision task, if subjects chose the delayed option, they received 16 Swiss francs by mail after the corresponding temporal delay. In the interpersonal decision task, if subjects chose the prosocial option, both they and the person at the corresponding social distance received  $1/10$  of the rewards provided by the chosen option (that is, 7.5 Swiss francs; the contact data of the other person were recorded after the experimental session).

**Transcranial magnetic stimulation.**

Subjects were stimulated either over the right pTPJ (22 subjects) or over the vertex (21 subjects) with standard cTBS (23). We used a Magstim Super Rapid stimulator (Magstim Co.) and a figure-of-eight coil with an internal diameter of 7 cm. For cTBS, bursts of three stimuli at 50 Hz were repeated with a frequency of 5 Hz for 40 s, resulting in a total of 600 pulses; stimulation intensity was set to 80% of the active motor threshold. The active motor threshold was defined as the lowest pulse intensity required to elicit a motor-evoked potential larger than 200  $\mu$ V on more than 5 of 10 trials from the contralateral first dorsal interosseous muscle while the subject was maintaining a contraction of about 20% maximum force (23). It has been shown that 40-s cTBS reduces the excitability of the stimulated brain region for about 60 min (23). Because the performance of the intertemporal and interpersonal decision tasks after the stimulation lasted about 13 min, we could be certain that the applied TMS protocol reduced the excitability of the stimulated region during the full period of task performance.

We determined stimulation sites using individual T1-weighted structural scans and Brainsight frameless stereotaxy (Rogue Research). In the pTPJ TMS condition, the coordinates for stimulation [peak MNI (Montreal Neurological Institute) coordinates:  $x = 60$ ,  $y = -58$ ,  $z = 31$ ] were taken from a previous functional magnetic resonance imaging study (9) that had found enhanced TPJ activation during prosocial relative to selfish choices in the interpersonal decision task. This region is part of the pTPJ area related to overcoming egocentricity (13). We transformed the pTPJ peak coordinates into the native space of each individual subject's structural scan using the parameter estimates for spatial normalization of the anatomical scan performed in SPM12. As a control site, we used the vertex, which was defined as the meeting point of the pre- and post-central sulcus in the intrahemi-

spheric fissure. The TMS coil was positioned tangentially to the cortical surface over these sites during stimulation, with the handle pointing in a posterior direction.

**Data analysis.**

The statistical analysis of the behavioral data was performed with MATLAB R2014b (MathWorks) and IBM SPSS Statistics 22. For both the intertemporal and the interpersonal decision task, we computed hyperbolic discount functions reflecting the discounted subjective value of the delayed and the prosocial reward depending on the temporal delay and the social distance, respectively. For that purpose, we first calculated individual indifference values in the two tasks. Each indifference value was defined as the point at which a subject chooses the delayed versus immediate reward or prosocial versus selfish reward with an equal probability of 50%. These indifference values were computed separately for each temporal delay in the intertemporal decision task and for each social distance in the interpersonal decision task. Specifically, using logistic regressions (function `glmfit` implemented in MATLAB), we predicted choices of the delayed reward in the intertemporal decision task by the amount of the immediate reward option, separately for all temporal delays. These logistic regressions resulted in  $\beta$  values for the constant term and for the regression weight of the logistic function. On the basis of the estimated logistic functions, we then determined indifference points as the values of the immediate reward at which each subject switched (that is, chose both options with a likelihood of 0.5) from predominantly choosing the immediate reward to predominantly choosing the delayed reward. The same was done to construct indifference values in the interpersonal decision task, resulting in six indifference values per task and subject. Finally, discount functions were fitted to these indifference values in both tasks (using the function `lsqcurvefit` in MATLAB), separately for each subject. We assumed that temporal and social discounting could be described by the following standard hyperbolic functions

$$SV_{\text{delay}} = V_{\text{delay}} / (1 + k_{\text{delay}} \times D_{\text{delay}}) \quad (1)$$

$$SV_{\text{social}} = V_{\text{social}} / (1 + k_{\text{social}} \times D_{\text{social}}) \quad (2)$$

where  $SV_{\text{delay}}$  and  $SV_{\text{social}}$  are the discounted values of the delayed and prosocial reward options, respectively, and  $V_{\text{delay}}$  and  $V_{\text{social}}$  are the intercepts of the discount functions.  $D_{\text{delay}}$  and  $D_{\text{social}}$  indicate the temporal delay or social distance, and  $k_{\text{delay}}$  and  $k_{\text{social}}$  represent subject-specific constants measuring the degree of temporal and social discounting. In temporal discounting, a larger  $k_{\text{delay}}$  parameter captures a higher number of immediate choices as temporal delays increase, whereas in social discounting, a larger  $k_{\text{social}}$  describes a higher number of selfish choices with increasing social distance. The intercepts  $V_{\text{delay}}$  and  $V_{\text{social}}$  as well as the discount parameters  $k_{\text{delay}}$  and  $k_{\text{social}}$  were free parameters and were determined separately for each subject by fitting Eqs. 1 and 2 to a subject's indifference points in the intertemporal and the interpersonal decision task, respectively. The start values for the parameters  $k_{\text{delay}}$  and  $k_{\text{social}}$  were set to 0.5, and the start values for  $V_{\text{delay}}$  and  $V_{\text{social}}$  were 160. The obtained parameter estimates were robust to these start values, because different start values resulted in the identical result pattern. In more detail, when we varied the initial values for the intercept parameter  $V$  from 0 to 160 (in steps of 10) and for the discount parameter  $k$  from 0 to 1 (in steps of 0.1), all parameter estimations revealed significant TMS effects on the discount parameters  $k_{\text{delay}}$  and  $k_{\text{social}}$  but not on  $V_{\text{delay}}$  and  $V_{\text{social}}$ .

The estimated parameters were log-transformed to normalize the skewed distributions of the parameters. Finally, we analyzed the log-transformed parameters with a mixed-measures ANOVA including the between-subject factor TMS (pTPJ versus vertex TMS) as well as the within-subject factors Task (intertemporal versus interpersonal decision task) and Parameter ( $V_{\text{delay}}$  versus  $k_{\text{delay}}$  and  $V_{\text{social}}$  versus  $k_{\text{social}}$ ).

## Study 2

### Participants.

Fifty-nine volunteers (30 female, 29 male;  $M_{\text{age}} = 24.1$ ,  $SD_{\text{age}} = 2.9$ ) participated in the study after they gave written informed consent. Three additional subjects were excluded. Two of them failed to follow task instructions by selecting persons they felt negatively about in the interpersonal decision task. The third did not understand the task instructions of the perspective-taking task, resulting in an unusually high error rate (mean error rate > 25% compared to a group average of 2%). Subjects were randomly assigned to the pTPJ TMS (20 subjects), vertex TMS (18 subjects), or S1 TMS (21 subjects) group.

### Task design.

Subjects performed the intertemporal and the interpersonal decision tasks in a similar way as in Study 1. However, unlike in Study 1, we controlled for any potential effects of the TMS manipulation on attentional reorienting (12) by presenting the temporal delay and social distance information by a vertical (instead of a horizontal) number line, in either ascending or descending order (counterbalanced across participants). Moreover, we presented the amounts of the immediate/selfish options on the left or the right side of the screen (again counterbalanced across subjects), whereas in Study 1 they appeared in the center of the screen (Fig. 3). We used the identical amounts of immediate, delayed, selfish, and prosocial rewards as in Study 1. Again, we used the social distances 1, 5, 10, 20, 50, and 100 in the interpersonal decision task, whereas in the intertemporal decision task we used shorter temporal delays (1, 10, 20, 50, 90, and 180 days) than in Study 1 to facilitate the payout procedure for delayed reward options.

Each trial of the intertemporal and interpersonal decision tasks started with the presentation of a central fixation cross for 3 s. Next, we displayed the temporal delay or social distance simultaneously with the immediate or selfish reward option to the left and right of the central fixation cross (5 s). During this period, subjects had to indicate their choices via key press. Subsequently, the next trial started.

In the perspective-taking task (25), we presented a room with 0 to 3 red discs displayed on the left and the right walls of the room. The discs were presented on one or on both walls. An avatar in the center of the room was facing either the left or the right wall. The task was to determine the number of discs either from one's own perspective or from the avatar's perspective. The avatar could see only the discs on the wall it was facing, whereas subjects could see the discs on both walls. Accordingly, the perspectives of the subject and of the avatar were either congruent (the subject and the avatar saw the same number of discs) or incongruent (the subject and the avatar saw a different number of discs; thus, the subject had to realize that the avatar saw fewer discs than did the subject because the avatar could not see the discs on the wall behind its back). The typical finding in this task is that subjects commit more errors in reporting the correct number of discs for incongruent relative to congruent perspectives. The incongruence effect is larger if subjects have to judge the avatar's perspective compared with their own perspective (25, 37), thereby showing that this task requires subjects to overcome their egocentricity bias.

Each trial of the perspective-taking task started with the presentation of a central fixation cross (1 s), followed by a cue (750 ms) indicating whether subjects should determine the number of discs from their own perspective ("self") or from the avatar's perspective ("other"). After the presentation of a further fixation cross for 500 ms, one digit (750 ms) appeared and specified the number of discs (0 to 3) for the subject to verify. Finally, the room showing the avatar and the discs was presented for 3 s. Subjects indicated whether the previously presented digit matched or mismatched the number of discs from the given perspective by pressing the left or right control key. The assignment of keys to match/mismatch responses was counterbalanced across subjects. Subjects performed one block of the perspective-taking task before (pre-TMS) and after TMS (post-TMS). Each block contained a total of 64 trials, with equal trial numbers for the combination of the factors Incongruence (congruent versus incongruent) and Perspective (self-perspective versus other-perspective).

After the post-TMS block of the perspective-taking task, subjects performed a paper-pencil version of the number line task, which served as a control task for potential TMS effects on number recognition (26). We presented subjects with four vertical number lines of 10-cm length. In two of them, the endpoints of the lines were defined as 0 and 180 (in analogy to the number of days used in the intertemporal decision task); in the other two, the endpoints were 0 and 100 (in analogy to the number of social distances used in the interpersonal decision task). The task was to estimate the number corresponding to a short horizontal line transecting the vertical number line. We measured performance in this task by calculating the mean difference (in percent) between the number estimated by the subjects and the true number at the transection line.

### TMS protocol and data analysis.

The stimulation protocol and analysis of the intertemporal and interpersonal decision tasks were identical to Study 1. However, in addition to the vertex TMS group, we also used an active TMS control site by applying TMS over the left S1. The TMS site for S1 was defined as 2 cm posterior to the individual subject's motor hotspot for the right hand, a site where TMS has been shown to have both behavioral and neural effects (38, 39). On the basis of Study 1, we expected pTPJ TMS, relative to vertex TMS and S1 TMS, to increase the discount parameters  $k_{\text{delay}}$  and  $k_{\text{social}}$ . We therefore tested these directed hypotheses using one-tailed  $t$  tests. In the perspective-taking task, we computed differences between error rates in the post-TMS and the pre-TMS block to test whether TMS changed performance in this task. These values were analyzed with a mixed-measures ANOVA including the between-subject factor TMS (pTPJ TMS versus S1 TMS versus vertex TMS) as well as the within-subject factors Perspective (self versus other) and Incongruence (congruent versus incongruent perspectives). Finally, we tested whether egocentricity bias (error incongruence effect for other-perspective minus error incongruence effect for self-perspective) predicted the steepness of temporal and social discounting. Using  $t$  tests, we assessed the hypotheses that the magnitude of egocentricity bias shows positive correlations with the log-transformed discount rates  $k_{\text{delay}}$  and  $k_{\text{social}}$ .

## SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at <http://advances.sciencemag.org/cgi/content/full/2/10/e1600992/DC1>

Supplementary Results

fig. S1. Fit of two-parameter hyperbolic discount functions [ $SV_{\text{delay}} = V_{\text{delay}}/(1 + k_{\text{delay}} \times D_{\text{delay}})$ ;  $SV_{\text{social}} = V_{\text{social}}/(1 + k_{\text{social}} \times D_{\text{social}})$ ] in Study 1.

fig. S2. Fit of two-parameter hyperbolic discount functions [ $SV_{\text{delay}} = V_{\text{delay}}/(1 + k_{\text{delay}} \times D_{\text{delay}})$ ;  $SV_{\text{social}} = V_{\text{social}}/(1 + k_{\text{social}} \times D_{\text{social}})$ ] in Study 2.

fig. S3. Illustration of TMS effects (pTPJ versus S1 versus vertex) on the differences between the number estimated by the subjects and the true number at the transection line relative to the total length of the number line (in percentage;  $\pm$ SEM) in the number line task.

## REFERENCES AND NOTES

- W. Mischel, Y. Shoda, P. K. Peake, The nature of adolescent competencies predicted by preschool delay of gratification. *J. Pers. Soc. Psychol.* **54**, 687–696 (1988).
- A. Boals, M. R. vanDellen, J. B. Banks, The relationship between self-control and health: The mediating effect of avoidant coping. *Psychol. Health* **26**, 1049–1062 (2011).
- K. Fujita, On conceptualizing self-control as more than the effortful inhibition of impulses. *Pers. Soc. Psychol. Rev.* **15**, 352–366 (2011).
- J. Metcalfe, W. Mischel, A hot/cool-system analysis of delay of gratification: Dynamics of willpower. *Psychol. Rev.* **106**, 3–19 (1999).
- B. Figner, D. Knoch, E. J. Johnson, A. R. Krosch, S. H. Lisanby, E. Fehr, E. U. Weber, Lateral prefrontal cortex and self-control in intertemporal choice. *Nat. Neurosci.* **13**, 538–539 (2010).
- S. M. McClure, D. I. Laibson, G. Loewenstein, J. D. Cohen, Separate neural systems value immediate and delayed monetary rewards. *Science* **306**, 503–507 (2004).
- Y. Morishima, D. Schunk, A. Bruhin, C. C. Ruff, E. Fehr, Linking brain structure and activation in temporoparietal junction to explain the neurobiology of human altruism. *Neuron* **75**, 73–79 (2012).
- G. Silani, C. Lamm, C. C. Ruff, T. Singer, Right supramarginal gyrus is crucial to overcome emotional egocentricity bias in social judgments. *J. Neurosci.* **33**, 15466–15476 (2013).
- T. Strombach, B. Weber, Z. Hangebrauk, P. Kenning, I. I. Karipidis, P. N. Tobler, T. Kalenscher, Social discounting involves modulation of neural value signals by temporoparietal junction. *Proc. Natl. Acad. Sci. U.S.A.* **112**, 1619–1624 (2015).
- R. Saxe, N. Kanwisher, People thinking about thinking people: The role of the temporoparietal junction in “theory of mind”. *Neuroimage* **19**, 1835–1842 (2003).
- C.-F. Chang, T.-Y. Hsu, P. Tseng, W.-K. Liang, O. J. L. Tzeng, D. L. Hung, C.-H. Juan, Right temporoparietal junction and attentional reorienting. *Hum. Brain Mapp.* **34**, 869–877 (2013).
- M. Corbetta, G. Patel, G. L. Shulman, The reorienting system of the human brain: From environment to theory of mind. *Neuron* **58**, 306–324 (2008).
- R. B. Mars, J. Sallet, F.-X. Neubert, M. F. S. Rushworth, Connectivity profiles reveal the relationship between brain areas for social cognition in human and monkey temporoparietal cortex. *Proc. Natl. Acad. Sci. U.S.A.* **110**, 10806–10811 (2013).
- H. Ersner-Hersfield, M. T. Garton, K. Ballard, G. R. Samanez-Larkin, B. Knutson, Don’t stop thinking about tomorrow: Individual differences in future self-continuity account for saving. *Judgm. Decis. Mak.* **4**, 280–286 (2009).
- D. Parfit, Personal identity. *Philos. Rev.* **80**, 3–27 (1971).
- B. A. Jones, H. Rachlin, Delay, probability, and social discounting in a public goods game. *J. Exp. Anal. Behav.* **91**, 61–73 (2009).
- B. Jones, H. Rachlin, Social discounting. *Psychol. Sci.* **17**, 283–286 (2006).
- T. Strombach, J. Jin, B. Weber, P. Kenning, Q. Shen, Q. Ma, T. Kalenscher, Charity begins at home: Cultural differences in social discounting and generosity. *J. Behav. Decis. Mak.* **27**, 235–245 (2014).
- B. Güroğlu, W. van den Bos, E. A. Crone, Sharing and giving across adolescence: An experimental study examining the development of prosocial behavior. *Front. Physiol.* **5**, 291 (2014).
- T. Suddendorf, M. C. Corballis, Mental time travel and the evolution of the human mind. *Genet. Soc. Gen. Psychol. Monogr.* **123**, 133–167 (1997).
- S. Baron-Cohen, A. M. Leslie, U. Frith, Does the autistic child have a “theory of mind”? *Cognition* **21**, 37–46 (1985).
- S. E. Lind, D. M. Bowler, Episodic memory and episodic future thinking in adults with autism. *J. Abnorm. Psychol.* **119**, 896–905 (2010).
- Y.-Z. Huang, M. J. Edwards, E. Rounis, K. P. Bhatia, J. C. Rothwell, Theta burst stimulation of the human motor cortex. *Neuron* **45**, 201–206 (2005).
- J. Jung, A. Bungert, R. Bowtell, S. R. Jackson, Vertex stimulation as a control site for transcranial magnetic stimulation: A concurrent TMS/fMRI study. *Brain Stimul.* **9**, 58–64 (2016).
- D. Samson, I. A. Apperly, J. J. Braithwaite, B. J. Andrews, S. E. Bodley Scott, Seeing it their way: Evidence for rapid and involuntary computation of what other people see. *J. Exp. Psychol. Hum. Percept. Perform.* **36**, 1255–1266 (2010).
- Z. Cattaneo, J. Silvanto, A. Pascual-Leone, L. Battelli, The role of the angular gyrus in the modulation of visuospatial attention by the mental number line. *Neuroimage* **44**, 563–568 (2009).
- T. A. Hare, S. Hakimi, A. Rangel, Activity in dlPFC and its effective connectivity to vmPFC are associated with temporal discounting. *Front. Neurosci.* **8**, 50 (2014).
- H. Ersner-Hersfield, G. E. Wimmer, B. Knutson, Saving for the future self: Neural measures of future self-continuity predict temporal discounting. *Soc. Cogn. Affect. Neurosci.* **4**, 85–92 (2009).
- S. Arzy, S. Collette, S. Ionta, E. Fornari, O. Blanke, Subjective mental time: The functional architecture of projecting the self to past and future. *Eur. J. Neurosci.* **30**, 2009–2017 (2009).
- W. van den Bos, C. A. Rodriguez, J. B. Schweitzer, S. M. McClure, Connectivity strength of dissociable striatal tracts predict individual differences in temporal discounting. *J. Neurosci.* **34**, 10298–10310 (2014).
- D. Laibson, Golden eggs and hyperbolic discounting. *Q. J. Econ.* **112**, 443–478 (1997).
- B. Reynolds, A review of delay-discounting research with humans: Relations to drug use and gambling. *Behav. Pharmacol.* **17**, 651–667 (2006).
- G. Hasler, Can the neuroeconomics revolution revolutionize psychiatry? *Neurosci. Biobehav. Rev.* **36**, 64–78 (2012).
- J. Monterosso, P. Piray, S. Luo, Neuroeconomics and the study of addiction. *Biol. Psychiatry* **72**, 107–112 (2012).
- G. Sansone, G. T. Fong, P. A. Hall, R. Guignard, F. Beck, U. Mons, M. Pötschke-Langer, H.-H. Yong, M. E. Thompson, M. Omar, Y. Jiang, Time perspective as a predictor of smoking status: Findings from the International Tobacco Control (ITC) Surveys in Scotland, France, Germany, China, and Malaysia. *BMC Public Health* **13**, 346 (2013).
- R. Yi, A. R. Buchhalter, K. M. Gatchalian, W. K. Bickel, The relationship between temporal discounting and the prisoner’s dilemma game in intranasal abusers of prescription opioids. *Drug Alcohol Depend.* **87**, 94–97 (2007).
- M. Schurz, M. Kronbichler, S. Weisengruber, A. Surtees, D. Samson, J. Perner, Clarifying the role of theory of mind areas during visual perspective taking: Issues of spontaneity and domain-specificity. *Neuroimage* **117**, 386–396 (2015).
- P. Tsang, M. F. Jacobs, K. G. H. Lee, M. J. Asmussen, C. M. Zapallow, A. J. Nelson, Continuous theta-burst stimulation over primary somatosensory cortex modulates short-latency afferent inhibition. *Clin. Neurophysiol.* **125**, 2253–2259 (2014).
- N. Valchev, B. Čurčić-Blake, R. J. Renken, A. Avenanti, C. Keyzers, V. Gazola, N. M. Maurits, cTBS delivered to the left somatosensory cortex changes its functional connectivity during rest. *Neuroimage* **114**, 386–397 (2015).

**Acknowledgments:** We thank E. Viganò and J. Ho for help with data acquisition.

**Funding:** This work was supported by grants PP00P1\_150739, 00014\_165884, and CRSII3\_141965 from the Swiss National Science Foundation. **Author contributions:** A.S., C.C.R., T.S., T.K., and P.N.T. designed the research; A.S. conducted the research; A.S. analyzed data; and A.S., C.C.R., T.S., T.K., and P.N.T. wrote the manuscript. **Competing interests:** The authors declare that they have no competing interests. **Data and materials availability:** All data needed to evaluate the conclusions in the paper are present in the paper and/or the Supplementary Materials. Additional data related to this paper may be requested from the authors.

Submitted 4 May 2016

Accepted 1 September 2016

Published 19 October 2016

10.1126/sciadv.1600992

**Citation:** A. Soutschek, C. C. Ruff, T. Strombach, T. Kalenscher, P. N. Tobler, Brain stimulation reveals crucial role of overcoming self-centeredness in self-control. *Sci. Adv.* **2**, e1600992 (2016).



This article is published under a Creative Commons license. The specific license under which this article is published is noted on the first page.

For articles published under [CC BY](#) licenses, you may freely distribute, adapt, or reuse the article, including for commercial purposes, provided you give proper attribution.

For articles published under [CC BY-NC](#) licenses, you may distribute, adapt, or reuse the article for non-commercial purposes. Commercial use requires prior permission from the American Association for the Advancement of Science (AAAS). You may request permission by clicking [here](#).

***The following resources related to this article are available online at <http://advances.sciencemag.org>. (This information is current as of October 20, 2016):***

**Updated information and services**, including high-resolution figures, can be found in the online version of this article at:

<http://advances.sciencemag.org/content/2/10/e1600992.full>

**Supporting Online Material** can be found at:

<http://advances.sciencemag.org/content/suppl/2016/10/17/2.10.e1600992.DC1>

This article **cites 39 articles**, 9 of which you can access for free at:

<http://advances.sciencemag.org/content/2/10/e1600992#BIBL>

*Science Advances* (ISSN 2375-2548) publishes new articles weekly. The journal is published by the American Association for the Advancement of Science (AAAS), 1200 New York Avenue NW, Washington, DC 20005. Copyright is held by the Authors unless stated otherwise. AAAS is the exclusive licensee. The title *Science Advances* is a registered trademark of AAAS