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Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans

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The precise localization of executive functions such as response inhibition within the prefrontal cortex (PFC), although theoretically crucial, has proven to be controversial and difficult[1]. Functional neuroimaging has contributed importantly to this debate[1–7], but as human cortical lesions are seldom discrete, the literature still lacks definitive neuropsychological evidence that a specific region is necessary for task performance. We overcame this limitation by using a new observer-independent method to relate the degree of damage within a specific prefrontal region to performance on a stop-signal task that is sensitive to the neurodevelopmental aspects of stopping behavior[2] and to attention-deficit/hyperactivity disorder (ADHD) as well as its amelioration by methylphenidate[5,8].

Go/no-go and stop-signal tasks require subjects to perform speeded responses on 'go' trials and to inhibit their response on 'no-go' or 'stop' trials. Such response inhibition usually activates a right-lateralized inferior frontal gyrus (IFG) region in neuroimaging studies[2–7] (**Fig. 1a**). We investigated whether this region is critical for response inhibition by studying the performance of patients with lesions of the right frontal lobe; if so, then the extent of damage to the right IFG, but not other regions of interest (ROIs), should correlate with task performance.

Eighteen patients (7 male, 17 right-handed, mean age 54.6 ± 9 years) with lesions of the right frontal lobe (9 aneurysm or hemorrhage, 9 excisions of meningioma; mean chronicity of lesion 3.2 ± 3.4 years) were selected from the Cambridge Cognitive Neuroscience Research Panel (CCNRP). Exclusion criteria were psychiatric diagnosis, color blindness or non-specific neurological disease. Patients were compared with 16 controls (8 male, 11 right-handed, mean age 53.7 years ± 10.7) matched on age ($t < 1$, n.s.) and predicted verbal IQ ($t < 1$, n.s). All subjects gave written informed consent, and the study was approved by the local research ethics committee.

For MRI scanning of patients' brains, we used three-dimensional set acquisition in the coronal plane using a SPGR T1-weighted sequence and a T2-weighted axial sequence. Lesions were traced using MRIcro (University of Nottingham, UK) and normalized to a standard template using SPM96 (Wellcome Department of Cognitive Neurology, London) with cost-function masking[9]. MRIcro was used to trace five ROIs: medial frontal (MED), orbital frontal gyrus (ORB), inferior frontal gyrus (IFG), middle frontal gyrus (MFG) and superior frontal gyrus (SFG) onto the standard SPM T1 template (**Fig. 1b**). The normalized lesion for each subject was superimposed onto each ROI to compute the volume of damaged gray matter for each brain region.

Response inhibition was tested using the stop-signal procedure[10] (**Fig. 2**). On each trial, a left- or right-pointing arrow stimulus was displayed on a computer screen. The subject responded with a left or right key press as quickly as possible (go task) unless they heard a beep (25% of trials, randomly dispersed), in which case they tried to withhold a response (stop task). The stop-signal delay (SSD) varied. Each subject performed five blocks of 64 trials each. This task gives a sensitive estimate of inhibitory control—the stop signal reaction time (SSRT)—reflecting the time it takes to internally suppress a response.

SSRT for right frontal patients was significantly slower than for controls (patients, 239 ± 78 ms; controls, 189 ± 46 ms; $t_{1,32} = 2.3$, $P < 0.05$). To test the specific hypothesis that the right IFG is critical for response inhibition, we correlated damage to each ROI with SSRT (**Fig. 3**). Correlations between SSRT and ROI damage were as follows: SFG ($n = 18$, $r = 0.34$, n.s), MFG ($r = 0.53$, $P = 0.025$), IFG ($r = 0.83$, $P < 0.0001$), ORB ($r = 0.30$, n.s.) and MED ($r = 0.51$, $P = 0.030$). Therefore, IFG damage seems to be particularly critical for response inhibition. This was confirmed as the strength of correlation between SSRT and IFG was significantly greater than between SSRT and any other ROI ($P < 0.05$ for all comparisons; test of non-independent correlations[11]). A further analysis explored the correlations between damage to IFG and other ROIs. These were as follows: SFG ($n = 18$, $r = 0.4$, n.s.), MFG ($r = 0.59$, $P = 0.01$), ORB ($r = 0.48$, n.s.) and MED ($r = 0.62$, $P = 0.007$). Common damage to IFG and other ROIs therefore possibly explained the significant correlations between SSRT and MFG and between SSRT and MED. This was confirmed using multiple regression to assess the correlation between SSRT and MFG while simultaneously controlling for damage to IFG (MFG coefficient, $t_{15} < 1$, n.s.), and the correlation between SSRT and MED while controlling for damage to IFG (MED coefficient, $t_{15} < 1$, n.s.). For both of these multiple regressions, damage to IFG significantly accounted for variability in SSRT. Although patients were significantly slower than controls to perform the go task (patients, 582 ± 136 ms; controls, 472 ± 70; $U = 75.0$, $P < 0.05$), the correlation between median no-signal RT

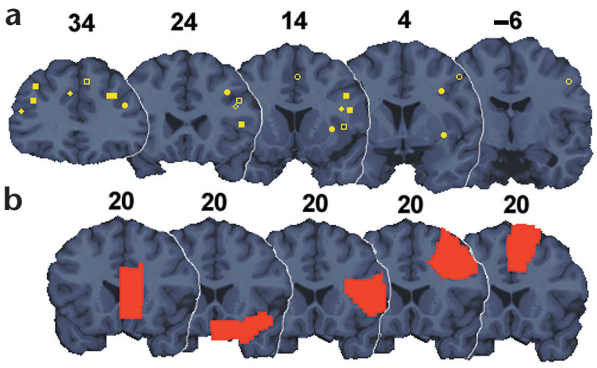

Fig. 1. Voxels activated by response inhibition in neuroimaging studies, and region of interest (ROI) approach of current study. (**a**) Coronal slices (y = 34, 24, 14, 4, –6) showing all Talairach coordinate foci reported in previous response inhibition studies: (■) Bunge *et al.* 2002, (□) Rubia *et al.* 1999, (●) Garavan *et al.* 1999, (○) Menon *et al.* 1999, (◆) Konishi *et al.* 1999 and (◆) Konishi *et al.* 1998. (**b**) ROIs in the present study, shown from left to right (y = 20): MED, ORB, IFG, MFG and SFG.

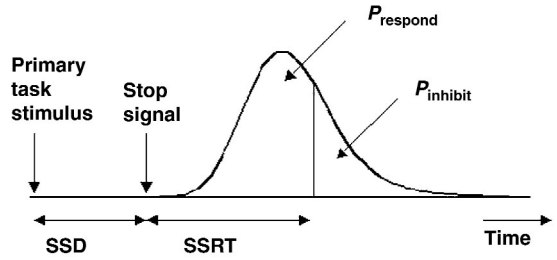

Fig. 2. Race-model estimation of SSRT[10]. A distribution of no-signal RTs (go trials) is shown beneath the curve. On stop trials, a tone occurs after the primary stimulus at a particular stop-signal delay (SSD). The stop signal divides the no-signal RT distribution into two probabilities: a left part consisting of responses fast enough to escape inhibition ($P_{respond}$) and a right part corresponding to $P_{inhibit}$. Provided SSD is varied to yield 50% $P_{inhibit}$ (the point of median no-signal RT), SSRT is estimable by subtracting average SSD from median no-signal RT. We ensured convergence to 50% $P_{inhibit}$ by using step-up and step-down interleaved staircases. If the subject inhibited successfully on a stop trial, then inhibition was made more difficult on the next stop trial by increasing the SSD by 50 ms; if the subject did not successfully inhibit on a stop trial, then SSD was decreased by 50 ms. Average SSD was computed from the values of four staircases after convergence on 50% $P_{inhibit}$.

and damage to IFG was not significant ($r = 0.14$), nor did median no-signal RT correlate reliably with SFG ($r = -0.29$), MFG ($r = 0.07$), ORB ($r = -0.38$) or MED ($r = -0.33$). Therefore, slowing of patients for the go task was not specifically due to damage of IFG or any other ROI, and probably did not account for the impact of IFG damage on SSRT estimation.

These findings were specific to the right frontal lobe as patients with left frontal cortex lesions had significantly faster SSRTs than did right frontal patients, and SSRT did not correlate significantly with damage to any ROI (see **Supplementary Fig. 1** online). A more detailed analysis of the right IFG used templates from the automated anatomical labeling (AAL) map[12]. Damage to the pars triangularis (Brodmann area 45) correlated significantly with SSRT (**Fig. 3**; $r = 0.65$, $P = 0.004$), as did damage to the pars opercularis (BA 44), but less so ($r = 0.57$, $P = 0.014$). Simultaneous multiple regression showed that damage to the pars triangularis significantly accounted for the variability in SSRT ($t = 2.2$, $P < 0.05$), whereas damage to the pars opercularis did not ($t = 1.4$, n.s.). Although our data strongly support the hypothesis that response inhibition is implemented uniquely by the right IFG (in particular, the pars triangularis), low variability in damage to ORB and MED for this sample leaves open the possibility that other foci may be critical.

These results show the utility of fMRI for generating hypotheses that are testable on patients. They provide important evidence for addressing the ongoing debate between the 'general purpose' view of PFC function[1] (that is, that executive functions are not readily localizable) and the 'modular' view that specific executive functions lie within discrete regions[13]. Our results certainly show that a specific executive function, response inhibition, can be localized to a discrete region of the PFC. Moreover, as neuroimaging studies have co-activated right IFG during response inhibition and other tasks such as cognitive set switching[7] or interference suppression[2], the right IFG may play a particular sort of inhibitory role across a range of tasks requiring suppression of response tendencies. Additionally, a specific role for the right IFG provides a strong basis for better understanding the neurodevelopment of stopping[2], the pathology of ADHD[5] and its amelioration by stimulant drugs[8].

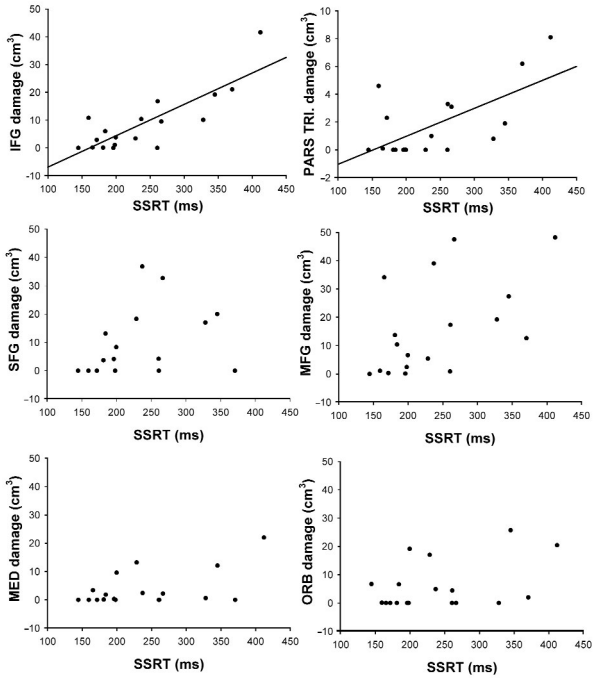

Fig. 3. Correlations between SSRT (ms) and the volume of damage to each region of interest (SFG, IFG, MFG, ORB, MED and pars triangularis, cm^3) for 18 patients. Damage to the right IFG was significantly correlated with SSRT, as was damage to the pars triangularis subregion of the IFG.

Note: Supplementary information is available on the Nature Neuroscience website.

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Competing interests statement

The authors declare that they have no competing financial interests.

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1. Duncan, J. & Owen, A.M. *Trends Neurosci.* **23**, 475–483 (2000).
2. Bunge, S.A., Dudukovic, N.M., Thomason, M.E., Vaidya, C.J. & Gabrieli, J.D.E. *Neuron* **33**, 301–311 (2002).
3. Menon, V., Adleman, N.E., White, C.D., Glover, G.H. & Reiss, A.L. *Hum. Brain Mapp.* **12**, 131–143 (2001).
4. Garavan, H., Ross, T.J. & Stein, E.A. *Proc. Natl. Acad. Sci. USA* **96**, 8301–8306 (1999).
5. Rubia, K. *et al. Am. J. Psychiatry* **156**, 891–896 (1999).
6. Konishi, S., Nakajima, K., Uchida, I., Sekihara, K. & Miyashita, Y. *Eur. J. Neurosci.* **10**, 1209–1213 (1998).
7. Konishi, S. *et al. Brain* **122**, 981–991 (1999).
8. Logan, G.D., Schachar, R.J. & Tannock, R. in *Attention and Performance XVIII* (eds. Monsell, S. & Driver, J.) 653–677 (MIT Press, Cambridge, Massachusetts, 2000).
9. Brett, M., Leff, A.P., Rorden, C. & Ashburner, J. *Neuroimage* **14**, 486–500 (2001).
10. Logan, G.D. in *Inhibitory Processes in Attention, Memory and Language* (eds. Dagenbach, D. & Carr, T.H.) 189–239 (Academic, San Diego, 1994).
11. Williams, E.J. *J. Roy. Stat. Soc. (Series B)* **21**, 396–399 (1959).
12. Tzourio-Mazoyer, N. *et al. Neuroimage* **15**, 273–289 (2002).
13. Goldman-Rakic, P. S. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **351**, 1445–1453 (1996).