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Stop-Signal Reaction-Time Task Performance: Role of Prefrontal Cortex and Subthalamic Nucleus

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The stop-signal reaction-time (SSRT) task measures inhibition of a response that has already been initiated, that is, the ability to stop. Human subjects classified as "impulsive," for example, those with attention deficit and hyperactivity disorder, are slower to respond to the stop signal. Although functional and structural imaging studies in humans have implicated frontal and basal ganglia circuitry in the mediation of this form of response control, the precise roles of the cortex and basal ganglia in SSRT performance are far from understood. We describe effects of excitotoxic fiber-sparing lesions of the orbitofrontal cortex (OF), infralimbic cortex (IL), and subthalamic nucleus (STN) in rats performing a SSRT task. Lesions to the OF slowed SSRT, whereas lesions to the IL or the STN had no effect. On the go-signal trials, neither cortical lesion affected go-trial reaction time (GoRT), but STN lesions speeded such latencies. The STN lesion also significantly reduced accuracy of stopping at all stop-signal delays, indicative of a generalized stopping impairment that was independent of the SSRT itself.

Keywords: infralimbic cortex, orbitofrontal cortex, prefrontal cortex, response inhibition, stop-signal reaction time, subthalamic nucleus

Introduction

It is often necessary to stop or change a behavioral response during its execution, to optimize the outcome. The stop-signal reaction-time (SSRT) task provides a paradigm for measuring this based on a "race" between 2 response tendencies, "going" and "stopping" (Logan and Cowan 1984; Logan 1994). The time required to stop a response in this way, the SSRT, is extensively used as a clinical index of inhibitory control, primarily in the study of attention deficit and hyperactivity disorder (ADHD), where impulsive subjects have slower SSRTs (Logan et al. 1997; Oosterlaan et al. 1998; Rubia et al. 1998). Indeed, disruption of executive functions leading to impaired behavioral inhibition may be a core deficit in ADHD (Barkley 1997), although a more integrative model has been proposed, which includes behavioral inhibition as one of several key executive function deficits within ADHD (Castellanos et al. 2006). Recent studies have extended use of the SSRT task to other disorders with impulsive symptoms, for example, Parkinson's disease (Gauggel et al. 2004), schizophrenia (Rubia, Russell, Bullmore, et al. 2001; Badcock et al. 2002; Rubia 2002), obsessive–compulsive disorder (Krikorian et al. 2004), and chronic cocaine (Fillmore and Rush 2002; Fillmore et al. 2002) or methamphetamine users (Monterosso et al. 2005).

Growing evidence implicates the frontal cortex and basal ganglia in stop-signal response control, and indeed interaction between the prefrontal cortex and basal ganglia may be essential for accomplishing response inhibition in the stop-signal task (Band and van Boxtel 1999). This hypothesis is supported by studies of lesions of the prefrontal cortex (Aron et al. 2003, 2004; Rieger et al. 2003; Rubia et al. 2003) or the basal ganglia (Eagle and Robbins 2003a, 2003b; Rieger et al. 2003; van den Wildenberg et al. 2006), with damage in each case leading to slower SSRTs. Indeed, in human subjects, slower SSRTs have been linked specifically with dysfunction of the right inferior frontal cortex, whereas damage to adjacent regions was not correlated with SSRT speed (Aron et al. 2003).

In addition to the "stop" response, prefrontal cortex and basal ganglia regions are implicated in the control of many other forms of behavioral inhibition, in human, primate, and rat studies (e.g., Fuster 1988). However, it is by no means clear whether subtypes of behavioral inhibition are mediated along shared or distinct neural pathways. For example, in human studies, the go/no-go task has revealed response inhibition deficits following frontal cortical damage (Drewe 1975; Decary and Richer 1995; Godefroy and Rousseaux 1996). However, neuroimaging studies have highlighted differential regional activity in the brain during the stop-signal task and the go/no-go task that implicates different mechanisms of control in the stop and no-go forms of inhibition (Band and van Boxtel 1999; Rubia et al. 1999; Rubia, Russell, Overmeyer, et al. 2001; Aron et al. 2003; Rubia et al. 2003). Similarly, in rodent studies, distinct regions of the prefrontal cortex have been implicated in the control of different subtypes of behavioral response control, for example, in the control of premature responding on the 5-choice serial reaction-time (5-CSRT) task or impulsive choice on a delayed reward task (Dalley et al. 2004). There are also regional differences within the basal ganglia in impulsive response mediation (Baunez and Robbins 1997; Cardinal et al. 2001; Christakou et al. 2001; Rogers et al. 2001).

We have previously shown regional differences within the basal ganglia with respect to SSRT task performance. Lesions within the dorsomedial striatum (DMStr), but not the nucleus accumbens (NAC) core, produce significant deficits in performance, including increased SSRTs. However, a potential site of cortical influence over SSRT task performance, and possible influence over DMStr-mediated inhibitory control, has yet to be found in the rat. Lesions of the prelimbic (PL) region of the rat medial prefrontal cortex did not affect any measure of performance on the SSRT task. This implies that PL–DMStr circuitry, which is involved in other forms of behavioral control, for example, responding on the 5-CSRT task (Christakou et al. 2001), does not influence SSRT task performance. Because the orbitofrontal cortex (OF) has recently been shown to output directly to the DMStr (Hoover and Vertes 2004; Groenewegen et al. 2005), this region may be a strong candidate for involvement in the stopping process. Both the OF and infralimbic cortex (IL) have been implicated in the control of behavioral inhibition (Dalley et al. 2004).

The STN is conventionally thought of as an output structure of the basal ganglia, acting as part of the indirect, potentially inhibitory, cortico-striato-thalamic circuitry. Current interest in its function during the stopping process has led to a hypothesis that it links more directly with regions of the cortex involved in stopping, providing rapid information processing during this form of inhibition. In human subjects, STN activation correlated with faster SSRTs (Aron and Poldrack 2006), and STN activation on the SSRT task also correlated with activation of the right inferior frontal gyrus, a region that has previously been associated with stopping (Aron et al. 2003). Additionally, SSRT deficits have been linked with abnormal STN function in Parkinson's disease (Gauggel et al. 2004), and stimulation within the STN, but not surrounding structures, in these patients improved SSRT (van den Wildenberg et al. 2006). Rat studies have shown striking similarities between the pattern of behavioral effects observed following damage to the STN and OF, which has led many to suggest that they participate in common circuitry involved in the regulation of certain forms of goal-directed and affective behavior (Winstanley et al. 2005).

Here, we describe the effects of excitotoxic fiber-sparing lesions of the OF, IL, and subthalamic nucleus (STN) in rats performing a SSRT task, in order to further examine the neural pathways that may be involved in processing the stop response.

Materials and Methods

Subjects

The subjects were 59 male Lister-hooded rats (Charles River, Margate, UK), weighing 240–275 g at the start of the study (week 1), 360–460 g at surgery (week 12), and 480–600 g at the end of the study (week 31). Rat weights were approximately 90% of the weights of free-feeding individuals, based on rat growth curves (Harlan, Bicester, UK). Rats were housed in groups of 4 animals, in environmentally enriched cages, under a reversed 12:12 h light:dark cycle (lights off at 07:30), and were tested during the dark phase of this cycle. During behavioral testing, weight gain was restricted (to approximately 1–2 g per week during the main experimental phase) by feeding with a total of 15–20 g of food per day (reinforcer pellets during the task plus laboratory chow), given 1–2 h after the end of the daily test session. Water was freely available except during testing. All experiments were conducted in accordance with the United Kingdom Animals (Scientific Procedures) Act, 1986.

Apparatus

All sessions were performed in 6 operant chambers (Med Associates, VT), each of which had 2 retractable levers, positioned 70 mm above the chamber floor and 80 mm to either side of a central food well (center-to-center measurement). A house light in the roof of the chamber remained on throughout the session. A pellet dispenser delivered 45 mg Noyes Formula P pellets (Sandown Scientific, Middlesex, UK) into the food well, and nose entry into the food well was monitored with an infrared detector. A center light, located above the food well, signaled reinforcement delivery. Lights above the left and right levers signaled presentation of their respective levers. A 4500-Hz Sonalert tone generator (Med Associates, Georgia, VT) was mounted high on the wall opposite to the levers and food well. Control of the chambers and online data collection were conducted using the Whisker control system (Cardinal and Aitken 2001), using the Cambridge Stop Task program, written by D.M.E. and J.M.C. England.

SSRT Task

The SSRT task for rats was derived from the task of Logan and Cowan (1984). This task provides an estimate of the time taken to stop a response, the SSRT, from measurable task parameters, the go-trial reaction-time (GoRT) distribution, and the accuracy of stopping on stop trials (Fig. 1*a–c*). The GoRT provides a measure of the speed of the go process and includes both reaction time (time required to release the left lever) and movement time (time required to move from left to right lever), which cannot be separated in this version of the task.

All rats were trained to perform the SSRT task following a training program that has been previously described in detail (Eagle and Robbins 2003a). Figure 1*d–h* shows the stop-task procedure. Trials were initiated with a nose-poke to the central food well, after which the left lever and left light were presented. A press on the left lever resulted in the right lever and right light being presented, and the left lever and left light were withdrawn/extinguished. Rats were trained to perform a rapid reaction-time response from left lever to right lever—the "go" response. Response speed was maintained by limiting the time for which the right lever was presented—the "limited hold" (LH, range 0.75–1.90 s, maintained at a constant value for each rat throughout the study. Lesion groups were matched for LH). During go trials, rats were rewarded with a pellet, delivered to the central food well, for pressing the right lever, but received a time-out of 5 s in darkness if they failed to press the right lever within the LH period. Following a correct trial, or the time-out period at the end of an incorrect trial, a nose-poke in the central food well initiated the next trial.

A stop-signal tone (40 ms, 4500 Hz) was presented on 20% of the trials at a predetermined time between the left and right lever presses. Stop trials were presented randomly within the session in order to discourage the rats from anticipating presentation of the stop trials. On stop trials, rats were required to initiate the same response as on go trials, but after hearing the stop signal, the rat was required to stop completion of the go response, that is, to refrain from pressing the right lever. The rat was required to withhold responding for the duration of a LH period, after which it was rewarded with a pellet. An incorrect response, which was a press on the right lever, resulted in a time-out of 5 s of darkness. On a few trials designated as stop trials, the rat responded on the right lever before the onset of the tone (more common for late tone presentations), and these trials were reclassified as go trials, in order to maintain the overall proportion of valid stop trials in each session at 20%. Rats performed one 20-min session per day, with a maximum of 200 trials per session.

Following initial training, rats received a baseline session (Zero Delay), during which the stop signal was presented as the left lever was pressed (i.e., with no delay between the onset of the go response and presentation of the stop signal). Mean GoRTs and stop-signal delays (SSDs) for each rat were calculated from 3 Zero-Delay sessions at the beginning of each experimental set. For each experimental set, SSD was changed between sessions but remained fixed within session. The following SSDs were presented in a randomized order: SSD = GoRT–600, GoRT–500, GoRT–400, GoRT–300, GoRT–200, GoRT–100 ms.

Experiment 1: Rats were tested before surgery with one experimental set of SSDs. Rats were then operated on and given 7 days recovery time postsurgery. Rats were given 15 days of Zero-Delay training to re-establish a stable baseline and then retested with one experimental set of SSDs.

Experiment 2: Extended LH challenge. At Zero Delay, where the stop signal was presented as the go response was initiated, the LH period on the stop trial was extended to challenge the ability of the rats to withhold responding for longer. This tested the ability of rats to withhold prepotent responding for an extended period of waiting. Rats were given 1 session of each of the following in order: LH × 1, LH × 2, LH × 3, and LH × 4.

Surgery

Rats were allocated to groups matched on baseline task performance of percent correct stop trials, percent correct go trials, SSRT, GoRT, and inhibition function shape. Rats received bilateral lesions to the OF (n = 14), IL (n = 14), STN (n = 18), or received sham surgery (infusion of vehicle only) (OF site, n = 5; IL site, n = 4; STN site, n = 4; total, n = 13). The data for the sham groups were compared for between-group differences, to determine if there were any site-specific effects of infusion site. When no between-group differences were found, these groups were subsequently combined into one sham–lesion group for comparison with the true lesion groups.

Different surgical protocols, in particular different neurotoxins, were used for cortical and STN lesions, based on the refinement of these procedures during previous studies. For example, ibotenic acid, while

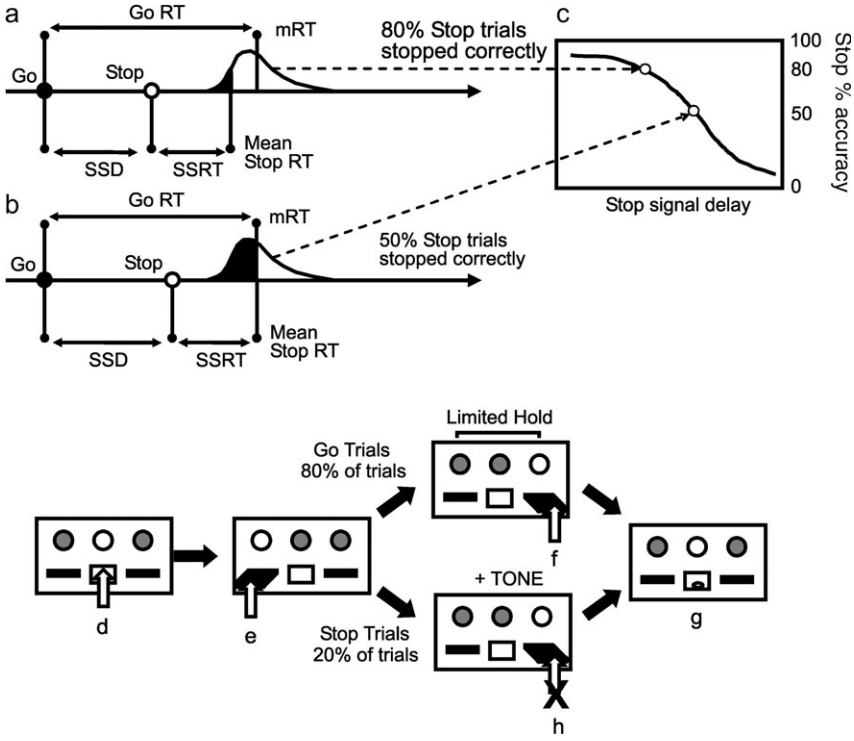

Figure 1. (*a–c*) Representation of the assumptions and predictions of the race model, showing how the probability of inhibition (*c*) depends on the distribution of the go-task reaction times, SSRT, and SSD. (*a*) The probability of inhibition (white) and the probability of response (failed inhibition, black) for a stop signal far away from completion of the go response. (*b*) The same probabilities when the stop signal is moved closer to completion of the go response and shows how fewer responses can be inhibited. (*d–h*) The stop task. A nose-poke in the central food well begins each trial (*d*). A press on the left lever begins the "go" response phase of the trial (*e*). The right lever is presented for a limited time, the LH, to promote rapid response. A right lever press (*f*) is rewarded (*g*). On "stop" trials, during the response phase of the trial (*e*), a tone is played. The rat must suppress response on the right lever to attain reward (*h*). Incorrect responses (failure to press on go trials or right lever press on stop trials) result in a time-out period.

producing discrete lesions within the STN, produces more extensive and less controllable tissue damage (producing large lacunae) during cortical lesion procedures than quinolinic acid.

For cortical surgery, rats were anesthetized with 5.0–8.0 mL Avertin (10 g 99% 2,2,2-tribromoethanol [Sigma-Aldrich, Dorset, UK]) in 5 mg tertiary amyl alcohol and 4.5 mL phosphate-buffered saline [PBS], in 40 mL absolute alcohol), administered intraperitoneally as 1.0 mL/100 g rat, to induce anesthesia, and then as 1.0-mL intraperitoneal injections over the course of the procedure to maintain anesthesia. Bilateral excitotoxic lesions of the OF or IL were made by infusion of 0.09 M quinolinic acid (Sigma-Aldrich), in PBS (pH = 7.4) through a 30-gauge stainless steel cannula connected via polyethylene tubing to a 10-μL glass Hamilton syringe in a microdrive pump. Lesion coordinates and toxin volumes for the OF were anterior (A) = +4.0 mm to bregma, lateral (L) = ±0.8 mm to the midline, and vertical (V) = −3.4 mm from dura (0.2 μL); (A) = +3.7 mm, (L) = ±2.0 mm, and (V) = −3.6 mm (0.3 μL); (A) = +3.2 mm, (L) = ±2.6 mm, and (V) = −4.4 mm (0.2 μL). Lesion coordinates and toxin volumes for the IL were (A) = +3.0 mm to bregma, (L) = ±0.7 mm to the midline, and (V) = −4.5 mm from dura (0.4 μL); (A) = +2.5 mm, (L) = ±0.7 mm, and (V) = −4.5 mm (0.4 μL). The incisor bar was set 2.3 mm below the interaural line. Infusions were made at a rate of 0.125 μL/min, with a further 3 min allowed for diffusion before the cannula was retracted, and the wound was cleaned and sutured. Sham-operated rats received identical infusions of PBS (pH = 7.4). Postoperatively, all rats were given 10 mL glucose saline intraperitoneally.

Bilateral excitotoxic lesions of the STN were made by infusion of ibotenic acid. All animals were anaesthetized with xylazine (15 mg/kg, intramurally) and ketamine (100 mg/kg, intramurally). Rats received bilateral injection of ibotenic acid (9.4 mg/mL, 0.053 M; Research Biochemicals, Illkirch, France; dissolved in 0.1 M phosphate buffer). The injection coordinates were taken as the average of interaural and bregma coordinates from the atlas of Paxinos and Watson (1986). Lesion coordinates and toxin volumes for the STN were: (A) = −3.8 mm to bregma, (L) = ±2.4 mm to the midline, and (V) = −8.35 mm from skull (0.5 μL). The incisor bar was set at −3.0 mm. Infusions were made over 3 min using a 10-mL Hamilton microsyringe connected by polyethylene tubing to a 30-gauge stainless steel injector. While recovering from anesthesia, STN-lesioned rats exhibit a short-lasting self-biting behavior that completely disappears when they have woken up. Therefore, protection of the paws was provided by bandaging and this was removed immediately after the animals had recovered from anesthesia.

Spontaneous Locomotor Activity

Spontaneous locomotor activity was measured postoperatively, between experiments 1 and 2, using 16 computerized photocell beam activity cages. The cages measured 25 × 40 × 18 cm with 2 photocell beams dividing the length of the cage into 3 equal parts. Each photocell beam was positioned 1 cm above the floor of the cage. An Acorn computer (Acorn Computers Ltd, Cambridge, UK) recorded activity during test sessions. The number of beam breaks was recorded over a 120-min period, separated into 5-min time bins. The position of subjects within the array of cages was randomized across experimental groups.

Statistical Analysis

Data are presented for each set of SSDs. All data were analyzed using SPSS 11.5, and graphs plotted using SigmaPlot 8.0 to show group means with error bars of ±1 standard error of the mean (SEM) unless otherwise stated.

Behavioral data were subjected to analysis of variance using a general linear model. All tests of significance were performed at $\alpha = 0.05$, and models were full factorial unless otherwise stated. Lesion group was a between-subjects factor. SSD was a within-subject, repeated-measures factor. Homogeneity of variance was verified using Levene's test. For repeated-measures analyses, Mauchly's test of sphericity was applied and the degrees of freedom corrected to more conservative values using the Huynh–Feldt epsilon for any terms involving factors in which the sphericity assumption was violated. Corrected degrees of freedom are

shown to the nearest integer. Following repeated-measures analyses, simple one-way analysis of variance or paired *t*-tests were used for analyses of within-subjects and between-subjects factors (for all post hoc analyses, α should be adjusted using Sidak's method ($\alpha' = 1 - (1 - \alpha)^{1/c}$, where c is the number of within-experiment analyses) (Howell 1997).

Correction for Omission Errors

The rationale for the analysis of SSRT and computation of the inhibition function is described in Logan (1994) and Eagle and Robbins (2003a). Omission errors, where the rat failed to respond at all, either voluntary or following distraction, may have occurred in the SSRT task. If these omissions occurred on stop-signal trials, the observed inhibition function would reflect both omissions and true response inhibition. The inhibition probability data were corrected for the occurrence of omissions using a procedure modified from Tannock et al. (1989) and Solanto et al. (2001):

$$\%(\text{inhibition})_{\text{corrected}} = \%(\text{inhibition})_{\text{observed}} - (\%(\text{nonresponse})_{\text{go}} - \%(\text{response})_{\text{stop (ZD)}})$$

Our modification includes an additional adjustment for the presence of task errors (i.e., incorrect responses from choosing to stop instead of go, or vice versa). Values for the "error" parameters could only be estimated from response distributions at Zero Delay and are assumed to remain constant across the range of SSDs, that is,

$$\%(\text{inhibition})_{\text{corrected}} = \%(\text{inhibition})_{\text{observed}} - ((\%\ \text{omissions} + \%\ \text{errors}) - \%\ \text{errors}).$$

Estimation of SSRT

SSRTs in this task were estimated using the protocol described in Logan (1994). Reaction times on go trials (on which no stop signal occurred) were rank ordered. We took the *n*th reaction time from the ranked list of go-trial reaction times for a particular delay session, where n was obtained by multiplying the number of reaction times in the distribution by the probability of responding on stop trials in the same session. This is an estimate of the time at which the stopping process finished, relative to the onset of the go signal. To estimate SSRT (the time at which stopping finished relative to the stop signal), SSD was subtracted from this value. This was done for each subject for each delay and the resulting mean taken for lesion and sham groups.

For example, in a session with 20 trials, 16 go trials (from which GoRT can be measured), 4 stop trials (1 correct stop and 3 incorrect stop; probability of correctly stopping = 0.25, therefore probability of responding [i.e., failing to stop] on stop trials = 0.75), stop signal presented 550 ms after the onset of the go stimulus, GoRTs 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900 ms.

To find the *n*th reaction time,

n = number of GoRTs × probability of responding on stop trials,

$n = (16 \times 0.75) = 12$,

12th reaction time in GoRT distribution = 860 ms.

Therefore, it is estimated that the stop process finished 860 ms after the onset of the go stimulus. If we subtract the delay to the stop signal from this value (860 – 550 = 310), we get an estimate of SSRT of 310 ms.

Histological Analysis

After behavioral testing had been completed, the rats were deeply anesthetized by intraperitoneal injection of 1.5–2.0 mL of sodium pentobarbitone (Euthatal; May and Baker, Harlow, UK) and were transcardially perfused with approximately 100 mL of PBS pH = 7.4, followed by 250 mL of formaldehyde solution (4% [w/v] paraformaldehyde in PBS). The brains were removed and postfixed in 4% (w/v) paraformaldehyde for 24 h and then transferred to 20% (w/v) sucrose in PBS until they sank. The tissue was serially sectioned at 60 μm on a freezing-stage sledge microtome, and a 1:6 series was mounted on slides. Sections were stained with Cresyl Violet and visualized microscopically under conventional bright field illumination, photographed digitally, and photomicrographs prepared using Adobe Photoshop Elements.

Results

Assessment of Lesions

Histological assessment of the extent and position of the lesions was carried out before analysis of the experimental data. Lesions were classified as acceptable if they showed significant damage or gliosis to the target area, with damage in both hemispheres, and no significant bilateral damage to the neighboring structures. From the original group, 3 rats (1 IL, 2 STN) failed to recover from anesthesia, and a further 8 rats were removed from the study because they had unilateral or misplaced lesions within the prefrontal cortex (OF, $n = 4$; IL, $n = 2$; control group with partial unilateral mechanical damage to IL region, $n = 2$). Nine rats were excluded from the STN group because they had significant, bilateral damage to the overlying zona incerta. The final number of rats in each group was OF, $n = 10$; IL, $n = 11$; STN, $n = 7$; and control, $n = 11$.

Figure 2 shows a diagrammatic reconstruction of the extent of all lesions. The center of the OF lesion common to all rats within that group was within the target ventral orbital (VO) and lateral orbital (LO) regions, with extensive neuronal loss and gliosis within these regions, with the lesion boundary extending to the ventral surface of the OF, and producing significant tissue shrinkage. Although there was some variability in the extent of the dorsal lesion boundary, neuronal damage toward the lesion boundary dorsal and medial to the VO/LO was incomplete, with sparing of cell bodies and reduced tissue shrinkage. The lesion started at approximately bregma +5.2 and included LO, VO, and, in some rats medial orbital (MO) cortices. Between bregma +4.7 and +3.7, there was unilateral encroachment into the PL cortex in 7 rats and unilateral encroachment into the anterior cingulate cortex in 5 rats. There was partial, unilateral, cannula track damage with some excitotoxic damage to the frontal association cortex in 7 rats. At the caudal level of the lesion (bregma +3.2), the lesion was centered in the boundary region between VO and LO. There was partial unilateral damage to the most medial extent of the insular cortex in 5 rats and partial damage to the most anterior ventrolateral extent of the IL in 5 rats. The OF lesions did not extend into the striatum or the NAcc.

Lesions to the IL produced extensive neuronal loss and gliosis within the IL, with the middle of the lesion common to all rats being centered within the borders of the IL: lesion damage extended to the medial surface of the IL in all cases, and rostrally there was slight encroachment into the ventral medial PL cortex and MO cortex. Lesion damage extended from bregma +3.7 to +2.2 mm, and there was almost complete neuronal loss within the IL at +3.2 and +2.7 mm from bregma. In 8 rats, the lesion extended into the dorsal peduncular cortex, and in one rat, there was slight damage to the most medial aspect of the anterior dorsal striatum. There was no damage to the NAcc.

For rats with lesions of the STN, the lesion consistently damaged at least 80% of STN and resulted in extensive gliosis and neuronal loss within the STN. The center of the STN lesion common to all rats was located within the dorsocentral STN. The STN lesions were located between bregma –3.6 and –4.3 mm. Two rats within the STN group had unilateral sparing of the medial 20% of the STN and 2 rats within the STN group

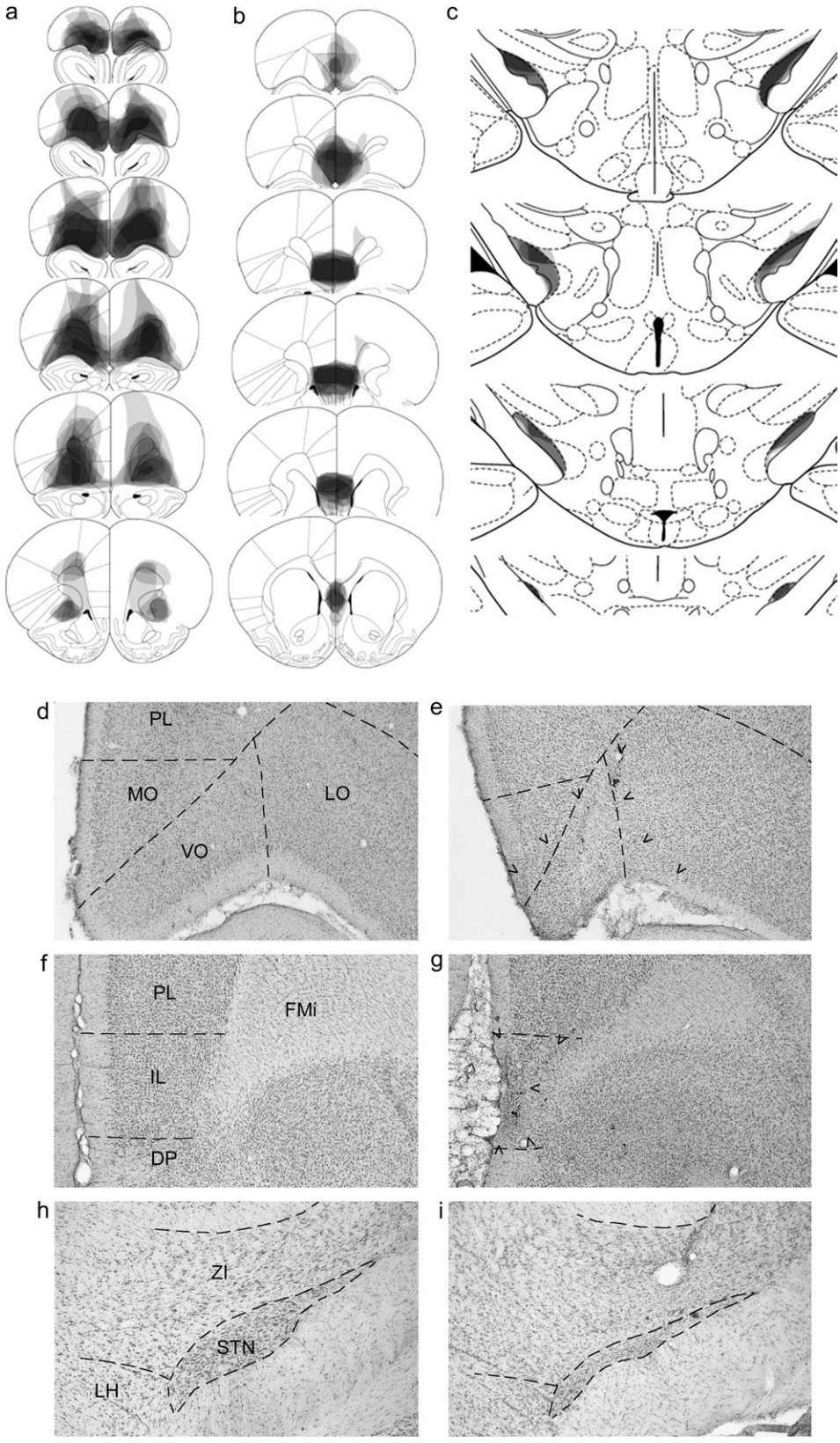

Figure 2. Schematic representation of bilateral excitotoxic lesions of (*a*) OF, (*b*) IL, or (*c*) STN. The extent of lesion damage for each rat is displayed. Graded shading represents the number of rats with lesion damage to each area, with the black areas representing the main locus of damage common to all lesions in the group and lighter shading representing fewer rats with damage in these regions (diagram adapted from Paxinos and Watson 1986). (*d–i*) Photomicrographs of Cresyl Violet–stained coronal sections of rat brains with lesions to (*e*) OF, (*g*) IL, or (*i*) STN and corresponding sham-operated control brains (*d*, *f*, *h*). The medial aspect of the section is toward the left of each figure. The approximate lesion boundaries in (*e*) and (*g*) are marked by arrowheads (>). In each case, the lesioned sections showed marked shrinkage of the target region. PL prelimbic cortex, MO medial orbital cortex, VO ventral orbital cortex, LO lateral orbital cortex, IL infralimbic cortex, DP dorsal penduncular cortex, FMi forceps minor corpus callosum, ZI zona incerta, LH lateral hypothalamic region.

had unilateral sparing of the medial 10% plus contralateral sparing of the lateral 10% of the STN (from visual assessment). There was slight unilateral lesion damage within part of the ventral zona incerta in 3 rats, but there was no damage to the adjacent lateral hypothalamus or to the entopeduncular nucleus.

We addressed the possible confound of "mass action" effects of larger lesions compared with smaller lesions with non-parametric correlation analysis of the relationship between the main task measures (SSRT, change in SSRT, GoRT, stop accuracy, go accuracy) and a rank ordering of lesion size. Lesions were rank ordered from the histological schematic of lesion size in Figure 2 by an independent observer, within each lesion group. There were no significant correlations between rank order of lesion size and any task measure for the range of lesion sizes within each group. When we considered all cortical lesions within one group, there was only a weak correlation between ranked lesion size and change in SSRT (Spearman rank correlation [$n = 21$] $r = 0.50$, $P < 0.05$).

Presurgical Performance

All rats showed normal inhibition functions, that is, they were better at inhibiting responses if the stop signal was presented far in advance of the completion of the go response, and they were worse at inhibiting responses if the stop signal was presented closer to the completion of the go response (SSD $F_{3,112} = 44.70$, $P < 0.001$). The delay-dependent inhibition was independent of go-trial accuracy, which did not change significantly across SSDs ($F_{4,125} = 1.17$, not significant [n.s.]; SSD × lesion $F_{11,125} = 0.94$, n.s.).

Preoperatively, the prospective lesion groups were matched by inhibition function, SSRT, GoRT, and baseline stop and go trial accuracy. Following removal of subjects with inappropriate lesion placement at the end of the experiment, there were still no significant baseline differences in preoperative performance between the lesion groups with respect to SSRT (although the OF group had slightly lower preoperative SSRTs as a result of removal of inappropriately lesioned rats, this difference was not significant. Fig. 3*a*, lesion $F_{3,35} = 1.06$, n.s.), GoRT (Fig. 3*c*, lesion $F_{3,35} = 0.98$, n.s.), inhibition function shape (lesion × SSD $F_{10,112} = 0.54$, n.s.), or baseline (no delay) stop and go trial accuracy (stop: lesion $F_{3,35} = 0.29$, n.s.; go: lesion $F_{3,35} = 0.46$, n.s.).

Postsurgical Performance

Postoperatively, the rats with sham (vehicle) infusions to each of the 3 different lesion sites were compared to assess if they could be treated as one group for further analysis. Within these control groups, there was no evidence that the site of vehicle infusion had any effect on the primary measures of SSRT (pre–post × site $F_{2,8} = 1.41$, n.s.), GoRT (pre–post × site $F_{2,8} = 1.24$, n.s.), or go-trial accuracy (pre–post × site $F_{2,8} = 1.03$, n.s.). Sham-operated rats were therefore treated as one group for subsequent analyses.

Effect on SSRT

There was a significant effect of excitotoxic lesions on SSRT (Fig. 3*a*; pre–post × lesion $F_{3,35} = 4.62$, $P < 0.01$). Further analysis indicated SSRT was significantly slower following lesions of the OF only (post hoc comparison between control and lesion

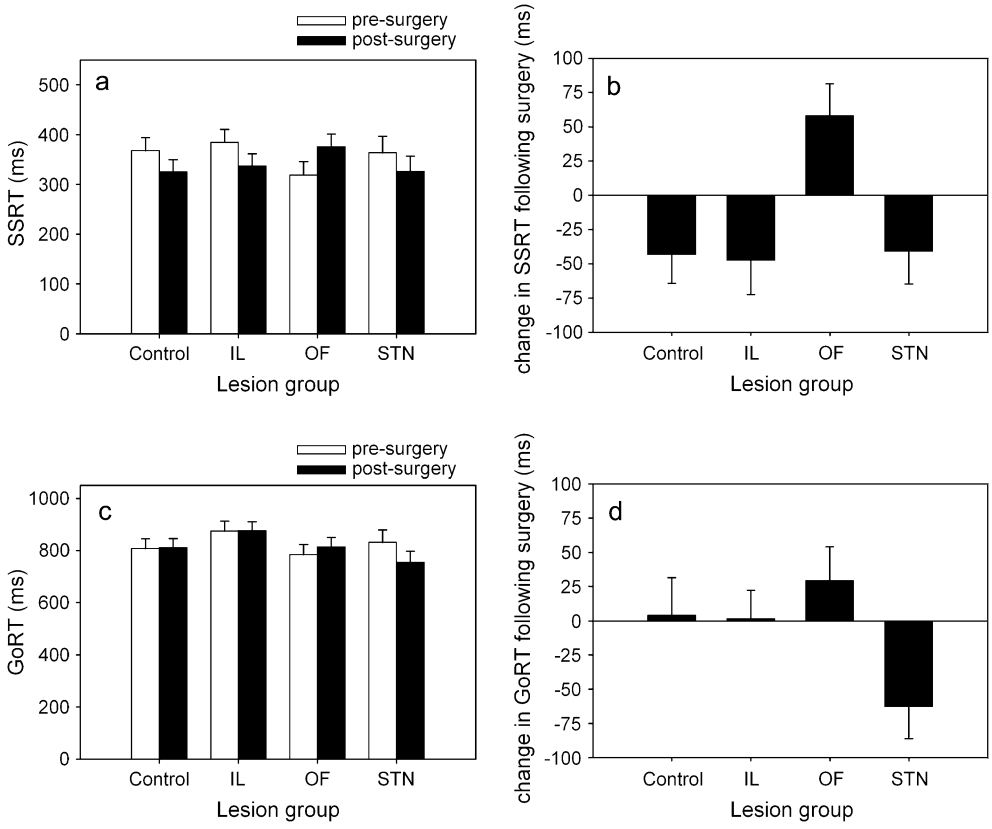

Figure 3. (*a*) SSRT and (*b*) change in SSRT following excitotoxic lesions or sham surgery. (*c*) GoRT and (*d*) change in GoRT following excitotoxic lesions or sham surgery. Vertical bars represent ±SEM.

group between presurgery and postsurgery—IL lesion × pre-post $F_{1,20} = 0.02$, n.s.; OF lesion × pre-post $F_{1,19} = 10.31$, $P < 0.01$; STN lesion × pre-post $F_{1,16} = 0.03$, n.s.). This differential lesion effect was further confirmed by analysis of the change in SSRT between presurgical and postsurgical test sessions (Fig. 3*b*; change in SSRT following surgery, lesion $F_{3,35} = 4.72$, $P < 0.01$, Dunnett's *t*-test for control—OF $P < 0.02$, control—IL and control—STN $P > 0.99$). Although there was a tendency for the SSRTs of the control rats to speed up between the presurgical and postsurgical tests, this effect was not significant (for control group pre-post $F_{1,10} = 4.20$, n.s.). In contrast, the OF group was slower following surgery (OF pre-post $F_{1,9} = 6.03$, $P < 0.05$).

Effects on GoRT

There was a different pattern of lesion effects on GoRT. There was a significant effect of excitotoxic lesions on GoRT (Fig. 3*c*; pre-post × lesion $F_{3,35} = 3.06$, $P < 0.05$). There was no effect of surgery on the GoRTs of the control rats (pre-post $F_{1,10} = 0.02$, n.s.), rats with IL lesions (pre-post $F_{1,10} = 0.004$, n.s.), or rats with OF lesions (pre-post $F_{1,9} = 1.39$, n.s.). However, the STN-lesioned rats had faster GoRTs following surgery (STN pre-post $F_{1,6} = 10.69$, $P < 0.017$). Figure 3*d* shows the change in GoRT following surgery for comparison with change in SSRT following surgery.

Effect on Stopping Performance

Although STN lesions did not affect SSRT per se, the stopping performance, represented by stop-trial accuracy, of STN-lesioned rats was significantly different from that of control rats. In particular, STN lesions impaired stopping when there was no delay between onset of the go trial and the stop signal (Fig. 4*a–d* left panels; pre-post × lesion $F_{3,35} = 4.08$, $P < 0.014$; control $F_{1,10} = 0.194$, n.s.; IL $F_{1,10} = 0.02$, n.s.; OF $F_{1,9} = 11.97$, $P < 0.01$; STN $F_{1,6} = 6.87$, $P < 0.05$). There was no effect of any lesion on the go-trial accuracy with no delay (go accuracy pre-post × lesion $F_{3,35} = 0.93$, n.s.). Stop-trial accuracy was also delay-independent for STN-lesioned rats, and their inhibition functions were abnormally flattened. Instead of showing the normal decrease in stopping performance as the stop signal was presented later in the trial, the STN-lesioned rats were consistently poor at stopping their response at all delays, that is, stop-trial accuracy was independent of delay (Fig. 4*a–d* middle panels; postsurgical SSD STN $F_{3,17} = 1.46$, n.s.; for all other groups, control $F_{4,40} = 18.53$; IL $F_{4,39} = 16.96$; OF $F_{4,36} = 8.72$, all $P < 0.01$). As a result of the combined deficits in stopping with no delay and across delays, there was no effect of the STN lesion on adjusted stop-trial accuracy, which attempts to control stop-trial accuracy for changes in baseline (no delay) performance that are unrelated to the speed of stopping and hence unrelated to SSRT (Fig. 4*d* right-hand panel, adjusted stop

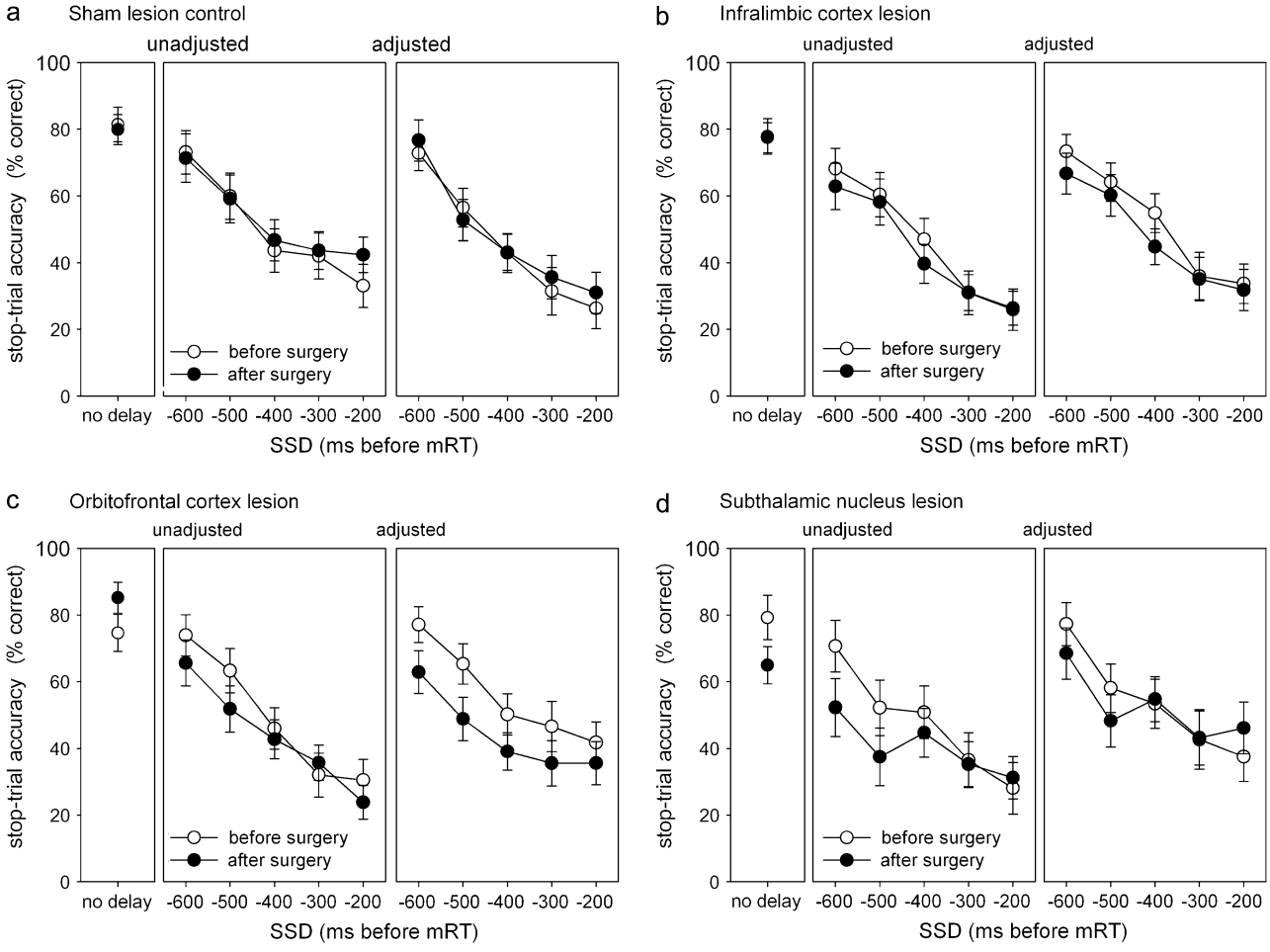

Figure 4. Accuracy on stop trials in sessions with no SSD (left panels: stop signal was presented as the left lever was pressed), across delays (center panels), and across delays with data adjusted for differences in baseline performance (right panels) for (*a*) control rats or following lesions to (*b*) IL, (*c*) OF, and (*d*) STN. Vertical bars represent ±SEM.

pre–post $F_{1,6}$ = 0.06, n.s.). In contrast, for the control and IL lesion groups, there was no significant change in stopping following surgery, either with no delay to the stop signal or across SSDs (adjusted stop control pre–post $F_{1,10}$ = 0.22; IL pre–post $F_{1,10}$ = 1.39, neither significant). Following OF lesions, there was an improvement in stopping performance when there was no delay to the stop signal, but stop-trial accuracy was actually worse across some delays, the combined action of which served to highlight a significant effect of OF lesions on adjusted stop performance (Fig. 4*c* right-hand panel, adjusted stop pre–post $F_{1,9}$ = 7.96, P < 0.02).

According to the race model (Logan 1994), correct estimation of SSRT is dependent upon subjects performing go trials as quickly as possible, yet attempting to stop whenever they hear the stop signal. In this case, the mean reaction time on incorrect stop trials should be significantly faster than the mean reaction time on correct go trials in a session because they fall within the left-hand side of the GoRT distribution (Fig. 1, black section of reaction-time distribution). If failure to stop is based on a rule that is not supported within the race model, then incorrect stop-trial reaction time would be similar to mean go-trial reaction time. Across all post-lesion delays, for control rats, the incorrect stop reaction time was significantly faster than correct go reaction time ($F_{1,10}$ = 7.54, P < 0.021), which conforms to the race model. For STN-lesioned rats, the incorrect reaction time was not significantly faster than correct go reaction time ($F_{1,6}$ = 0.89, n.s.). This suggests that the stopping performance of rats with STN lesions did not conform to the requirements of the race model for accurate estimation of SSRT.

Lengthening LH with no SSD – effects on ability to withhold responding

Single-session challenges increased the LH period for the stop trials so that the rats were required to withhold responding for 2, 3, and 4 times the normal LH period. All rats were less able to withhold responding as the LH length increased (Fig. 5; LH $F_{2,70}$ = 42.90, P < 0.001). Throughout this challenge, the rats with STN lesions were significantly worse at stopping (lesion $F_{3,35}$ = 4.05, $P \leq 0.014$, Dunnett's t-test control—STN $P \leq 0.011$, all others n.s.). However, although the STN-lesioned rats were generally impaired in stopping, they remained sensitive to changes in the LH. There were no significant differences between lesion groups in the ability to withhold responding when the LH was extended (lesion × LH $F_{6,70}$ = 0.89, n.s.; control LH $F_{2,17}$ = 10.71, $P \leq 0.01$; IL LH $F_{2,18}$ = 19.10, P < 0.001; OF LH $F_{2,22}$ = 11.62, P < 0.01; STN $F_{2,13}$ = 6.08, $P \leq 0.011$).

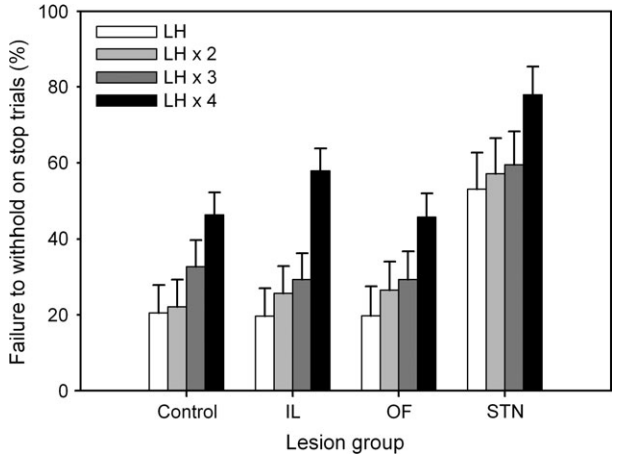

Figure 5. Extended LH challenge. Across 4 sessions, rats received stop trials in which the LH was extended so that the rat was required to withhold responding for up to 4 times the normal LH period. In all sessions, stop trials were presented with no SSD. Vertical bars represent ± SEM.

Spontaneous Locomotor Activity

Rats with STN lesions showed higher levels of spontaneous locomotor activity than control subjects, as measured by the number of beam breaks during the 120-min test session. Neither the OF lesions nor the IL lesions affected spontaneous locomotor activity (Fig. 6; lesion $F_{3,35}$ = 6.13, P < 0.01; Dunnett's test, STN $P \leq 0.011$; OF P > 0.5, n.s.; IL P > 0.5, n.s.).

Discussion

This study has shown, for the first time, that excitotoxic, fiber-sparing, lesions of a region of the rat prefrontal cortex can impair the ability to stop a response that has already been initiated, that is, the SSRT. SSRT was significantly slower following OF lesions, whereas there was no impairment following IL lesions. Even though OF-lesioned rats showed an improvement in no-delay stopping accuracy, when delays were introduced, stopping was impaired. The deficit induced by OF lesions was also highly specific to the speed of the stop response: the speed of the go response was not impaired by OF lesions, nor was there a change in spontaneous locomotor activity. Additionally, there was no effect of OF lesions on response control during an extended LH test. This manipulation may induce a form of impulsivity having more in common with no-go trials on the go/no-go task, or with the extended intertrial interval (ITI) test in the 5-CSRT task, in neither of which OF-lesioned rats were impaired (Chudasama et al. 2003). Although the IL lesion produced no significant effects on any measure in the SSRT task, this group showed the greatest percentage change in ability to withhold responding of all the groups (38% change in ability to withhold at 4-times normal LH for the IL group compared with 25% for the control group), perhaps comparable with IL lesion–induced premature responding during longer ITIs on the 5-choice task (Chudasama et al. 2003). The specificity of the effect of OF lesions to SSRT, coupled with

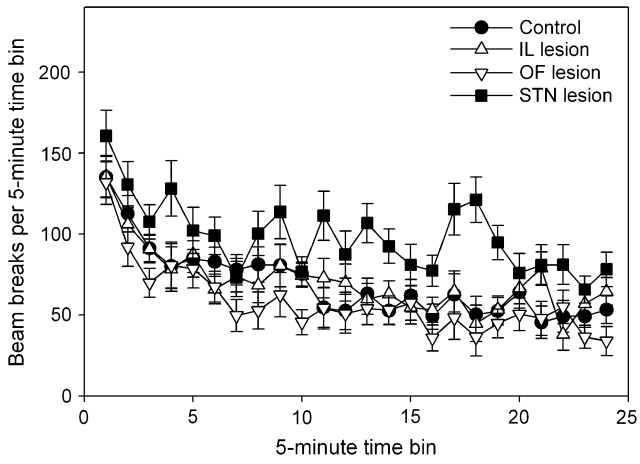

Figure 6. Spontaneous locomotor activity. Infrared beam breaks are shown for 5-min time bins over the 2-h session. Vertical bars represent ±SEM.

evidence of only a weak correlation between the SSRT impairment and relative cortical lesion size compared with the effect of lesion position, supports the conclusion that lesion position, rather than lesion size, was responsible for the differences in effects of OF and IL lesions within this study.

The functional dissociability of regions of the rat cortex in the SSRT task is not surprising, given the different roles of the OF and PL/IL in the rat during other tests of response control. For example, in the 5-CSRT task, rats with OF lesions made more perseverative responses following a correct response. By contrast, IL lesions did not affect perseverative responding, instead increasing impulsive premature responding (Chudasama et al. 2003). In a test of impulsive choice, the delayed reward task, OF lesions appeared to reduce impulsive choice: lesioned rats chose a small, immediate reward less often than control rats (Winstanley et al. 2004). Although IL lesions were not tested on this task per se, a combined IL/PL (medial prefrontal cortex) lesion had very different effects on performance of this task, rendering the rats generally insensitive to delay (Cardinal et al. 2004). These data are consistent with a role for the IL in behaviors requiring a subject to withhold from responding, whereas the OF has a clear role in other forms of response control, such as stopping, or inhibiting perseveration.

Lesions of the STN produced effects that were markedly different from the effects of either cortical lesion, with a profound impairment in stopping across all delays, a general speeding of the GoRT and increased spontaneous locomotor activity. The deficit in accuracy was specific to the stop process, leaving go-trial accuracy unaffected. This stopping impairment was also found during the extended LH test, although there was no change in the relative ability to withhold responding with extended delay. However, when data were adjusted for any no-delay stop-accuracy impairment, no subsequent slowing of SSRT was found.

Impaired stopping following STN lesions might not relate primarily to SSRT, but to more fundamental processing of the stop signal itself, or to the balance in response selection between stopping and going, impairments that fall outside the capacity of the race model (Logan and Cowan 1984). If STN-lesioned rats performed stop trials according to the assumptions of the race model (Logan and Cowan 1984), there should have been no impairment in stop-trial accuracy with no delay to the stop signal, and the mean reaction times of failed stop trials should have been significantly faster than the overall mean of correct go trials, falling to the left of the reaction time distribution for all correct go trials (Fig. 1, black section of reaction-time distribution). Following STN lesions, no-delay stop-trial accuracy was significantly impaired, and failed stop-trial reaction times were not significantly different from GoRTs, implying that rats with STN lesions were equally poor at stopping on slow GoRT trials as on fast GoRT trials. This validates the hypothesis that STN lesions induced a failure to correctly activate the stopping process rather than a slowing of SSRT per se.

STN-lesioned rats might either be more motivated to earn reward or to perseverate with responses associated with reward, as demonstrated by increased break points on progressive ratio schedules, increased conditioned locomotor activity for food, and increased delay tolerance on a delayed reward task (Baunez et al. 2002; Winstanley et al. 2005). Therefore, rats with STN lesions may be more highly motivated to perform a prepotent response for a reward, and consequently, be poorer at initiating inhibition of that response, leading to both the stop-accuracy deficits and the speeding of GoRT exhibited by the rats in this study.

It is of critical significance to other studies of SSRT task performance that failure to recognize such a profound baseline performance deficit could lead to a misdiagnosed impairment in SSRT because, for example, both attentional impairments and slower SSRTs would produce a decrease in stop-trial accuracy across delays. Indeed, subjects with schizophrenia showed baseline performance deficits that impaired stopping in the absence of SSRT changes (Badcock et al. 2002), although, in general, studies of human subjects do not monitor baseline changes in responding on no-delay stop trials. Nevertheless, an important deficit following STN damage might be impaired baseline stopping accuracy rather than slower SSRT.

There is considerable evidence consistent with a role for the STN in processes of response selection and attention, both in human and rat subjects. For example, in rats, STN lesions reduced accuracy and increased premature responding in the 5-CSRT task (Baunez and Robbins 1997; Baunez et al. 2001; Winstanley et al. 2005). In examples from human studies, patients with Parkinson's disease made more errors in a no-go condition than controls (Cooper et al. 1994), indicating a response inhibition deficit in these patients that was similar to the effects of STN lesions in our study. van den Wildenberg et al. (2006) suggested that deficient response selection processes in Parkinson's disease may benefit from stimulation to the STN during performance of the stop-signal paradigm.

Although our findings do not preclude a role for the STN in the stopping process, the transformations that were required in order to calculate SSRT using the race model may have obscured any SSRT slowing following STN lesions because the race model does not make any provision for differences in baseline levels of responding. Indeed, there is significant support for STN involvement in the stopping process in the study by Aron and Poldrack (2006), which found that STN activation correlated with faster SSRTs. Importantly, as the Aron and Poldrack study did not investigate abnormal STN function, there was no potential interference in their results from differences between subjects in baseline performance, although the relationship between STN activity and baseline levels of attentional accuracy was not assessed. It is clear that further research is required to clarify the role of the STN in SSRT processes, in particular in Parkinson's disease where the function of the STN is impaired.

Specificity of Corticobasal Ganglia Circuitry to SSRT

This study supports the existence of discrete regions of functional dissociation that extend beyond the cortex, throughout the basal ganglia, and that differentially mediate the control of subtypes of impulsive responding. More specifically, the stopping process may be mediated along a discrete orbitofrontal–DMStr pathway in the rat because SSRT deficits can be induced by both OF lesions and lesions of the DMStr (Eagle and Robbins 2003a). The ventral OF, which was the main locus of damage common to all of the OF lesions in the current study, projects mainly to the DMStr, but not to the core region of the NAC (Hoover and Vertes 2004; Groenewegen et al. 2005), lesions of which had no effect on SSRT (Eagle and Robbins 2003b).

In contrast, there were no effects on the SSRT task of lesions of either IL or PL medial prefrontal lesions, regions of the prefrontal cortex that also project to the DMStr, but that project

more strongly to the shell and core subregions of the NAC, respectively (Kelley 2004; Voorn et al. 2004). Indeed, there was no effect on any component of the SSRT task following lesions of the IL or the PL, nor of the PL ventral striatal output site, the NAC core (Eagle and Robbins 2003b). The role of the NAC shell in impulsive responding has yet to be investigated.

Although OF–DStr circuitry has been implicated in other forms of behavioral control, such as the moderation of perseverative responding on the 5-CSRT task (Rogers et al. 2001; Chudasama et al. 2003), this type of behavioral disinhibition has also be linked to dysfunction within the PL–DMStr circuitry (Christakou et al. 2001). Impaired stopping appears, thus far, to be one form of behavioral dysfunction that is highly specific to the OF–DMStr circuitry. Indeed, differences between the effects of OF and DMStr lesions on this task, primarily the lack of effect of OF lesions on GoRT, reinforce the specificity of the OF–DMStr pathway to the stopping process alone.

In summary, OF, but not IL, lesions induced selective SSRT-slowing effects in the rat that allow functional comparisons to be made between this region of the rat prefrontal cortex and the right inferior frontal cortex in human subjects. Impaired SSRT has been strongly linked with impaired function of the right inferior frontal cortex in human subjects (Aron et al. 2003; Rubia et al. 2003). Given our present state of anatomical knowledge, it would be imprudent to suggest that the OF in rats is homologous to the right inferior frontal cortex in humans. However, these regions have proven, so far, to be the only prefrontal cortical regions in their respective subjects to be implicated in the control of SSRT, strong functional similarities that merit further study.

The SSRT-specific deficit induced by OF lesions supports the existence of an OF–DMStr pathway that mediates this form of response control. The profound and distinctive effects of STN lesions on this task suggests that the STN does not act simply as a motor output for this OF–DMStr circuitry but instead has the ability to fundamentally affect baseline response selection or attention. This may have implications for the interpretation of SSRT task data in patients with cortical or basal ganglia dysfunction.

Notes

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References

Aron AR, Fletcher PC, Bullmore ET, Sahakian BJ, Robbins TW. 2003. Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. Nat Neurosci. 6:115–116.

Aron AR, Poldrack RA. 2006. Cortical and subcortical contributions to stop signal response inhibition: role of the subthalamic nucleus. J Neurosci. 26:2424–2433.

Aron AR, Robbins TW, Poldrack RA. 2004. Inhibition and the right inferior frontal cortex. Trends Cogn Sci. 8:170–177.

Badcock JC, Michie PT, Johnson L, Combrinck J. 2002. Acts of control in schizophrenia: dissociating the components of inhibition. Psychol Med. 32:287–297.

Band GPH, van Boxtel GJM. 1999. Inhibitory motor control in stop paradigms: review and reinterpretation of neural mechanisms. Acta Psychol. 101:179–211.

Barkley RA. 1997. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull. 121:65–94.

Baunez C, Amalric M, Robbins TW. 2002. Enhanced food-related motivation after bilateral lesions of the subthalamic nucleus. J. Neuroscience 22(2):562–568.

Baunez C, Humby T, Eagle DM, Ryan LJ, Dunnett SB, Robbins TW. 2001. Effects of STN lesions on simple vs choice reaction time tasks in the rat: preserved motor readiness, but impaired response selection. Eur J Neurosci. 13:1609–1616.

Baunez C, Robbins TW. 1997. Bilateral lesions of the subthalamic nucleus induce multiple deficits in an attentional task in rats. Eur J Neurosci. 9:2086–2099.

Berendse HW, Galisode Graaf Y, Groenewegen HJ. 1992. Topographical organization and relationship with ventral striatal compartments of prefrontal corticostriatal projections in the rat. J. Comp. Neurol. 316:314–347.

Cardinal RN, Aitken MRF. 2001. Whisker, version 2.2, computer software.

Cardinal RN, Pennicott DR, Sugathapala CL, Robbins TW, Everitt BJ. 2001. Impulsive choice induced in rats by lesions of the nucleus accumbens core. Science. 292:2499–2501.

Cardinal RN, Winstanley CA, Robbins TW, Everitt BJ. 2004. Limbic corticostriatal systems and delayed reinforcement. Ann N Y Acad Sci. 1021:33–50.

Castellanos FX, Sonuga-Barke EJ, Milham MP, Tannock R. 2006. Characterizing cognition in ADHD: beyond executive dysfunction. Trends Cogn Sci. 10:117–123.

Christakou AK, Robbins TW, Everitt BJ. 2001. Functional disconnection of medial prefrontal cortex and medial caudate-putamen: effects on performance on a visual attention task in the rat. Brain Cogn. 47:35–37.

Chudasama Y, Passetti F, Rhodes SE, Lopian D, Desai A, Robbins TW. 2003. Dissociable aspects of performance on the 5-choice serial reaction time task following lesions of the dorsal anterior cingulate, infralimbic and orbitofrontal cortex in the rat: differential effects on selectivity, impulsivity and compulsivity. Behav Brain Res. 146:105–119.

Cooper JA, Sagar HJ, Tidswell P, Jordan N. 1994. Slowed central processing in simple and go/no-go reaction time tasks in Parkinsons's disease . Brain 117(3):517–529.

Dalley JW, Cardinal RN, Robbins TW. 2004. Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates. Neurosci Biobehav Rev. 28:771–784.

Decary A, Richer F. 1995. Response selection deficits in frontal excisions. Neuropsychologia. 33:1243–1253.

Drewe E. 1975. Go–no go learning after frontal lobe lesions in humans. Cortex. 11:8–16.

Eagle DM, Robbins TW. 2003a. Inhibitory control in rats performing a stop-signal reaction-time task: effects of lesions of the medial striatum and d-amphetamine. Behav Neurosci. 117:1302–1317.

Eagle DM, Robbins TW. 2003b. Lesions of the medial prefrontal cortex or nucleus accumbens core do not impair inhibitory control in rats performing a stop-signal reaction time task. Behav Brain Res. 146:131–144.

Fillmore MT, Rush CR. 2002. Impaired inhibitory control of behavior in chronic cocaine users. Drug Alcohol Depend. 66:265–273.

Fillmore MT, Rush CR, Hays L. 2002. Acute effects of oral cocaine on inhibitory control of behavior in humans. Drug Alcohol Depend. 67:157–167.

Fuster JM. 1988. The prefrontal cortex. Anatomy, physiology and neuropsychology of the frontal lobe. 2nd ed. New York: Raven Press.

Gauggel S, Rieger M, Feghoff TA. 2004. Inhibition of ongoing responses in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 75:539–544.

Godefroy O, Rousseaux M. 1996. Divided and focused attention in patients with lesion of the prefrontal cortex. Brain Cogn. 30:155–174.
Groenewegen HJ, Schilman EA, Joel D, Uylings HBM. 2005. The orbitofrontal cortex in rats projects to central parts of the caudate-putamen and to a lesser extent to the ventral striatum. Washington (DC): Society for Neuroscience, Online.
Hoover WB, Vertes RP. 2004. Efferent projections of the ventral frontal polar cortex. San Diego (CA): Society for Neuroscience, Online.
Howell DC. 1997. Statistical methods for psychology. 4th ed. Belmont (CA): Duxbury Press.
Krikorian R, Zimmerman ME, Fleck DE. 2004. Inhibitory control in Obsessive-Compulsive Disorder. Brain Cogn. 54:257–259.
Logan GD. 1994. On the ability to inhibit thought and action. A users' guide to the stop signal paradigm. In: Dagenbach D, Carr TH, editors. Inhibitory processes in attention, memory and language. San Diego (CA): Academic Press. p. 189–236.
Logan GD, Cowan WB. 1984. On the ability to inhibit thought and action—a theory of an act of control. Psychol Rev. 91:295–327.
Logan GD, Schachar RJ, Tannock R. 1997. Impulsivity and inhibitory control. Psychol Sci. 8:60–64.
Monterosso JR, Aron AR, Cordova X, Xu J, London ED. 2005. Deficits in response inhibition associated with chronic methamphetamine abuse. Drug Alcohol Depend. 79:273–277.
Oosterlaan J, Logan GD, Sergeant JA. 1998. Response inhibition in AD/HD, CD, comorbid AD/HD+CD, anxious, and control children: a meta-analysis of studies with the stop task. J Child Psychol Psychiatry. 39:411–425.
Paxinos G, Watson C. 1986. The rat brain in stereotaxic coordinates. II ed. London: Academic Press.
Rieger M, Gauggel S, Burmeister K. 2003. Inhibition of ongoing responses following frontal, nonfrontal, and basal ganglia lesions. Neuropsychology. 17:272–282.
Rogers RD, Baunez C, Everitt BJ, Robbins TW. 2001. Lesions of the medial and lateral striatum in the rat produce differential deficits in attentional performance. Behav Neurosci. 115:799–811.
Rubia K. 2002. The dynamic approach to neurodevelopmental psychiatric disorders: use of fMRI combined with neuropsychology to elucidate the dynamics of psychiatric disorders, exemplified in ADHD and schizophrenia. Behav Brain Res. 130:47–56.
Rubia K, Oosterlaan J, Sergeant JA, Brandeis D, von Leeuwen T. 1998. Inhibitory dysfunction in hyperactive boys. Behav Brain Res. 94:25–32.
Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SCR, Simmons A, Bullmore ET. 1999. Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. Am J Psychiatry. 156:891–896.
Rubia K, Russell T, Bullmore ET, Soni W, Brammer MJ, Simmons A, Taylor E, Andrew C, Giampietro V, Sharma T. 2001. An fMRI study of reduced left prefrontal activation in schizophrenia during normal inhibitory function. Schizophr Res. 52:47–55.
Rubia K, Russell T, Overmeyer S, Brammer MJ, Bullmore ET, Sharma T, Simmons A, Williams SC, Giampietro V, Andrew CM, et al. 2001. Mapping motor inhibition: conjunctive brain activations across different versions of go/no-go and stop tasks. Neuroimage. 13:250–261.
Rubia K, Smith AB, Brammer MJ, Taylor E. 2003. Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. Neuroimage. 20:351–358.
Solanto MV, Abikoff H, Sonuga-Barke E, Schachar R, Logan GD, Wigal T, Hechtman L, Hinshaw S, Turkel E. 2001. The ecological validity of delay aversion and response inhibition as measures of impulsivity in AD/HD: a supplement to the NIMH multimodal treatment study of AD/HD. J Abnorm Child Psychol. 29:215–228.
Tannock R, Schachar RJ, Carr RP, Chajczyk D, Logan GD. 1989. Effects of methylphenidate on inhibitory control in hyperactive-children. J Abnorm Child Psychol. 17:473–491.
van den Wildenberg WP, van Boxtel GJ, van der Molen MW, Bosch DA, Speelman JD, Brunia CH. 2006. Stimulation of the subthalamic region facilitates the selection and inhibition of motor responses in Parkinson's disease. J Cogn Neurosci. 18:626–636.
Voorn P, Vanderschuren LJMJ, Groenewegen HJ, Robbins TW, Pennartz CMA. 2004. Putting a spin on the dorsal-ventral divide of the striatum. Trends in Neurosciences 27(8):468–474.
Winstanley CA, Baunez C, Theobald DE, Robbins TW. 2005. Lesions to the subthalamic nucleus decrease impulsive choice but impair autoshaping in rats: the importance of the basal ganglia in Pavlovian conditioning and impulse control. Eur J Neurosci. 21:3107–3116.
Winstanley CA, Theobald DE, Cardinal RN, Robbins TW. 2004. Contrasting roles of basolateral amygdala and orbitofrontal cortex in impulsive choice. J Neurosci. 24:4718–4722.