

Inhibition of subliminally primed responses is mediated by the caudate and thalamus: evidence from functional MRI and Huntington's disease

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Summary

Masked prime tasks have shown that sensory information that has not been consciously perceived can nevertheless trigger the preactivation of a motor response. Automatic inhibitory control processes prevent such response tendencies from interfering with behaviour. The present study investigated the possibility that these inhibitory control processes are mediated by a cortico-striatal-pallidal-thalamic pathway by using a masked prime task with Huntington's disease patients (Experiment 1) and with healthy volunteers in a functional MRI (fMRI) study (Experiment 2). In the masked prime task, clearly visible left- or right-pointing target arrows are preceded by briefly presented and subsequently masked prime arrows. Participants respond quickly with a left or right key-press to each target. Trials are either compatible (prime and target pointing in the same direction) or incompatible (prime and target pointing in different directions). Prior behavioural and electrophysiological results show that automatic inhibition of the initially primed response tendency is reflected in a 'negative compatibility effect' (faster reaction times for incompatible trials than for compatible trials), and is shown to consist of three distinct processes (prime activation, response inhibition and response conflict) occurring within 300 ms. Experiment 1 tested the hypothesis that lesions of the striatum would interrupt automatic inhibitory control by study-

ing early-stage Huntington's disease patients. Findings supported the hypothesis: there was a bimodal distribution for patients, with one-third (choreic) showing disinhibition, manifested as an absent negative compatibility effect, and two-thirds (non-choreic) showing excessive inhibition, manifested as a significantly greater negative compatibility effect than that in controls. Experiment 2 used fMRI and a region of interest (ROI) template-based method to further test the hypothesis that structures of the striatal-pallidal-thalamic pathway mediate one or more of the processes of automatic inhibitory control. Neither prime activation nor response conflict significantly engaged any ROIs, but the response inhibition process led to significant modulation of both the caudate and thalamus. Taken together, these experiments indicate a causal role for the caudate nucleus and thalamus in automatic inhibitory motor control, and the results are consistent with performance of the task requiring both direct and indirect striatal-pallidal-thalamic pathways. The finding that Huntington's disease patients with greater chorea were disinhibited is consistent with the theory that chorea arises from selective degeneration of striatal projections to the lateral globus pallidus, while the exaggerated inhibitory effect for patients with little or no chorea may be due to additional degeneration of projections to the medial globus pallidus.

Keywords: priming; striatum; motor control; subliminal; compatibility

Abbreviations: fMRI = functional magnetic resonance imaging; ISI = interstimulus interval; NCE = negative compatibility effect; ROI = region of interest; UHDRS = Unified Huntington's Disease Rating Scale

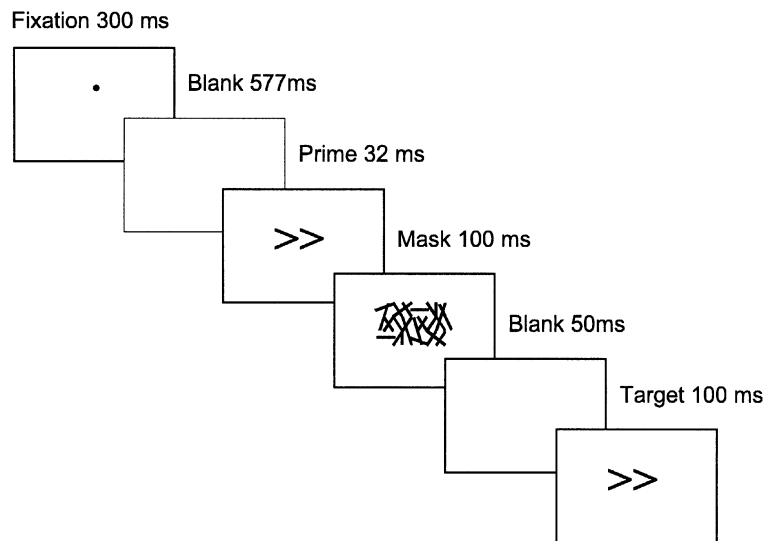


Fig. 1 Experimental trial design for compatible ISI-150 trial. Trials were ‘compatible’ when prime and target arrows pointed in the same direction, ‘incompatible’ when they pointed in opposite directions, and ‘neutral’ when the prime was a plus sign. In ISI-0 blocks, targets appeared together with (above or below) the mask, i.e. with an ISI of 0 ms after the prime. In ISI-150 blocks, targets appeared 150 ms after offset of the mask, i.e. with an ISI of 150 ms after the prime.

Introduction

In a continually changing environment, organisms must be able to identify relevant information quickly, and to select and execute a corresponding response rapidly. Interruption of ongoing motor activity must also be feasible in case a sudden environmental change requires instant response modification. Therefore, even sensory information having no immediate relevance to a current task must be processed to a level where it can influence performance. Numerous studies have shown that human motor processes are affected by such irrelevant information (e.g. Coles *et al.*, 1985; Gratton *et al.*, 1988; Miller and Hackley, 1992; Eimer, 1995), and even by stimuli which have not been consciously perceived (subliminal response priming) (Klotz and Wolff, 1995; Schlaghecken and Eimer, 1997; Dehaene *et al.*, 1998; Eimer and Schlaghecken, 1998; Eimer, 1999). Such effects have been attributed to the operation of ‘direct perceptuo-motor links’ (Neumann and Klotz, 1994), which enable perceptual information to act directly on the motor system once the respective stimulus–response mapping has been established.

Since such direct perceptuo-motor links are not subject to voluntary control, they might trigger response tendencies that are inappropriate in a given task context. To maintain adaptive behaviour, such response tendencies need to be actively inhibited. The present studies investigated the neural basis of this activation-followed-by-inhibition process. We employed the masked prime paradigm (Fig. 1), which has already been shown to be a useful tool for the study of motor activation and inhibition (Eimer, 1999; Eimer and Schlaghecken, 1998, 2001; Schlaghecken and Eimer, 2000, 2001).

Participants responded with a left or right key-press to a simple visual target. On each trial, the target was preceded by a masked prime stimulus, which was assigned to the same response as the subsequent target (compatible trial), to the opposite response (incompatible trial), or to no response (neutral trial). Previous studies have demonstrated that when the target is presented immediately after the prime [prime–target interstimulus interval (ISI) of 0 ms], behavioural costs (longer reaction times, more errors) are present for incompatible trials, and benefits (shorter reaction times, fewer errors) are observed for compatible trials relative to neutral trials [the positive compatibility effect (PCE)]. However, when the interval between prime and target is increased (to ≥ 80 ms), performance costs are elicited for compatible trials, and benefits for incompatible trials [the negative compatibility effect (NCE)]. These priming effects are best understood on the basis of EEG recordings used to derive the lateralized readiness potential (an electrophysiological index of unimanual response preparation) (Eimer, 1999; Eimer and Schlaghecken, 1998).

Figure 2 shows grand averaged lateralized readiness potential waveforms elicited on compatible, neutral and incompatible trials, generated from previously published data (Eimer and Schlaghecken, 1998) using behavioural procedures identical to those used in the present experiments. An initial activation of the response to the prime around 200 ms after prime onset (A) resulted in partial activation of the correct response on compatible trials and the incorrect response on incompatible trials. About 100 ms later, this initial activation reversed and was replaced by a partial

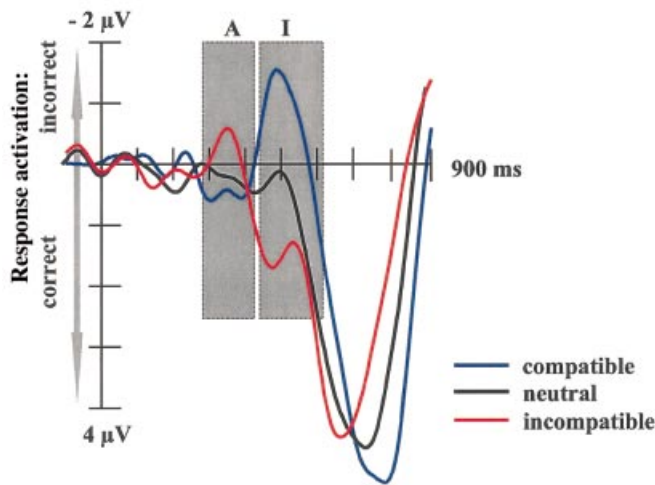


Fig. 2 Lateralized readiness potential from a prior EEG study demonstrating response facilitation (A) and inhibition (I) processes during masked priming. Activation of the correct response for any given trial (the response assigned to the target) is indicated by positive (downward-going) deflections, while incorrect response activation is reflected by negative (upward-going deflections). See Introduction for detailed explanation.

activation of the opposite response (I), reflecting the inhibition of the initial response tendency. For neutral trials, neither initial activation nor subsequent inhibition was observed. The PCE is elicited when response selection takes place during the initial activation phase (when the interval separating primes and targets is short). In this case, there is a response conflict on incompatible trials because the incorrect response is preactivated, while there is facilitation on compatible trials because the correct response is preactivated. By contrast, an NCE results when response selection happens during the subsequent inhibitory phase (when prime–target intervals are increased). In this case, there is a response conflict on compatible trials because the response required by the target is already subject to inhibition, whereas there is facilitation on incompatible trials because it is not. Such behavioural effects are obtained in spite of participants' inability to perceive consciously masked primes, as evidenced by chance performance in forced choice blocks (Eimer and Schlaghecken, 1998).

An early clue to the identity of brain structures involved in the activation-followed-by-inhibition process came from the observation that unilateral subthreshold repetitive transcranial magnetic stimulation of the motor and premotor cortex slowed reaction times but did not affect the pattern of PCEs and NCEs (Schlaghecken *et al.*, 2001). Therefore we assumed the activation-followed-by-inhibition process was mediated by brain structures operating functionally prior to the premotor or motor cortex. Structures within the cortico-striatal-pallidal-thalamic loops are good candidates for exerting selective control over competing response tendencies (De Jong *et al.*, 1995).

If this hypothesis holds, then subjects with basal ganglia disorders should show abnormal NCE profiles on the masked priming task. Here we studied patients with early-stage Huntington's disease, an inherited progressive neurodegenerative disorder of typically mid-life onset, characterized clinically by motor dysfunction, cognitive deterioration and psychiatric symptoms, and caused, at least in the early stages, by cell death in the striatum (Vonsattel and DiFiglia, 1998; Rosas *et al.*, 2001). As patients with Huntington's disease have well-established deficits in a variety of other forms of inhibition, including the suppression of saccades (Lasker *et al.*, 1987; Tsai *et al.*, 1995), overcoming stimulus–response incompatibility (Georgiou *et al.*, 1995) and prepulse inhibition (Swerdlow and Geyer, 1998), we supposed that an abnormal NCE profile for Huntington's disease patients might be due specifically to impaired response inhibition.

The objective of the second experiment was to test further the hypothesis that structures within the striatal-pallidal-thalamic circuitry are specifically implicated in the activation-followed-by-inhibition process by employing event-related functional MRI (fMRI). We used healthy volunteers alone as scanning Huntington's disease patients would pose significant problems because of head movement. We used fMRI to separate the neural correlates of response inhibition from those of prime activation or response conflict, even when these processes followed each other in very close temporal succession (within ~300 ms) (Fig. 2). We predicted that if the Huntington's disease patients showed an abnormal NCE, and if this was due to a compromised inhibitory process, then we might localize response inhibition to the striatum in healthy controls.

Experiment 1

Methods

Participants

Fifteen patients with early-stage clinically symptomatic and genetically confirmed Huntington's disease and 15 healthy age- and IQ-matched volunteers participated (for demographic information see Table 1). All subjects gave informed consent, and the patient study was approved by the Cambridgeshire Health Authority Local Research Ethics Committee. Seven of the patients were taking one or more forms of medication: five were taking a selective serotonin reuptake inhibitor, three were taking anti-dopaminergic medication, two were taking a tricyclic antidepressant, and one person was taking anti-epileptic medication.

Task

Prime stimuli were left- and right-pointing double arrowheads and plus signs (<<, >>, ++). Only arrow stimuli served as targets. Stimuli subtended a visual angle of approximately

Table 1 Measuring response inhibition using the NCE: Huntington's disease patients with greatest chorea have abolished NCEs, those with little chorea have exaggerated NCEs

	No. of subjects	Age (years)	IQ	NCE	UHD	Chorea	Rigidity	Duration (years)
A: group results								
HD	15	50 (7)	114 (7.5)	-15.9 (11.5)				
CTRL	15	49 (8.7)	114 (6.6)	-16.1 (4.1)				
B: subgroup results								
HD-PCE	5	52.0 (2.3)	116.7 (2.4)	36.3 (7.6)	14.8 (2.7)	6.8* (2.3)	1.0 (0.5)	5.0 (0.55)
HD-NCE	10	49.4 (2.5)	113 (3.0)	-42.0 [†] (8.3)	18.7 (4.4)	1.7 (0.6)	1.0 (0.3)	6.2 (1.3)

Mean (standard error) indices are shown for age, IQ (predicted verbal score on National Adult Reading Test), overall clinical score (UHD) from the UHDRS, the chorea and rigidity subscores from the UHDRS, years since first symptoms (Duration) and the NCE (median reaction time, incompatible minus compatible at ISI = 150 ms). (A) Compared with controls, the Huntington's disease (HD) patients do not have a significantly different NCE, but are significantly more variable ($P < 0.01$). (B) HD-PCE denotes PCE instead of NCE; HD-NCE denotes exaggerated NCE. *HD-NCE patients have significantly more movement than HD-PCE patients ($Z = 2.1$, $P < 0.05$); [†]HD-NCE patients have significantly exaggerated NCEs relative to the 10 controls with most exaggerated NCEs ($P = 0.050$).

1° × 1°. Masks were constructed from a 6 × 5 matrix, randomly filled with overlapping lines of different length and orientation. A new random mask was constructed on each trial. Stimuli were black on a white background.

Each trial started with a fixation dot at the centre of the screen for 300 ms (Fig. 1). A prime was presented for 32 ms at fixation, 577 ms after the offset of the fixation dot, and this was followed immediately by a mask (100 ms). Targets were presented for 100 ms, slightly above or below the mask. On 'compatible' trials, prime and target arrows pointed in the same direction, while on 'incompatible' trials they pointed in opposite directions.

The interval between prime and target (the ISI) was set at 150 ms in order to maximize the effect of the inhibitory process (see Introduction). Participants were given a button-box for right and left index finger responses, interfaced to a computer running ERTS software (Berisoft Corporation, Frankfurt, Germany) with 0.6 ms resolution for recording responses. Participants were instructed to maintain central eye fixation and to respond as fast and accurately as possible with a left button-press to a left-pointing target arrow and with a right button-press to a right-pointing target arrow. After a practice block of 20 trials, each participant performed 120 compatible and 120 incompatible trials (randomized, and with counterbalancing of the factors target direction, target position and prime-target compatibility). For the statistical analysis, an index of activation-followed-by-inhibition was produced by subtracting median correct reaction times of compatible trials from median correct reaction times of incompatible trials.

Results

Table 1A shows that, overall, there was no difference for the NCE measure between Huntington's disease patients (-15.9

± 44.5 ms, SD) and controls (-16.1 ± 15.8 ms, SD), ($U = 99.0$, $Z < 1$). However, Huntington's disease patients were significantly more variable than controls ($F = 9.9$, $P < 0.01$), and this was due, upon inspection, to a subset of patients showing PCE instead of NCE (i.e. a mean PCE of +36.3 ms) (Fig. 3). Subsequent analysis revealed this subset (Huntington's disease-PCE) to be significantly worse ($Z = 2.1$, $P < 0.05$) than the remainder of the Huntington's disease patients (Huntington's disease-NCE) on a neurological measure of chorea, as measured by the Unified Huntington's Disease Rating Scale (UHDRS) (Table 1B).

Of the five patients in group Huntington's disease-PCE, only two were taking medication, making it unlikely that this was the cause of the difference with respect to the Huntington's disease-NCE group. Importantly, the mean NCE for the Huntington's disease-NCE group (10 subjects) was -42.0 ms compared with -24.2 ms for the same proportion of controls (10 subjects) showing a maximum NCE. This was a significant difference ($U = 25$, $Z = 1.9$, $P = 0.050$, two-tailed, non-parametric test), indicative of excessive response inhibition in the group Huntington's disease-NCE.

Discussion

The finding that choreic patients had abolished NCEs is consistent with this subgroup displaying a disinhibition syndrome, as demonstrated by impaired performance on numerous cognitive tasks (Lasker *et al.*, 1987; Georgiou *et al.*, 1995; Tsai *et al.*, 1995; Swerdlow and Geyer, 1998). However, the finding of an exaggerated NCE in non-choreic subjects was unexpected. It suggests overactive inhibitory control, more in keeping with parkinsonian rigidity. It is well known that clinical features in Huntington's disease may be variable, and a 'rigid' variant is observed in both juveniles and

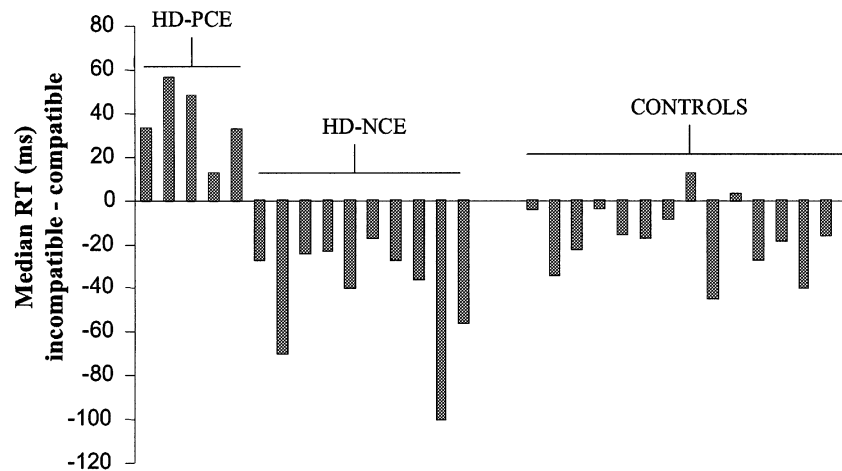


Fig. 3 Reaction time (RT) data for patients with Huntington's disease compared with healthy controls. The graphic shows that the distribution of patients' data is bimodal: some patients [Huntington's disease-PCE (HD-PCE)] show an absent negative-compatibility effect (NCE), indicative of disinhibition; other patients [Huntington's disease-NCE (HD-NCE)] show the NCE but it is exaggerated relative to controls, indicative of overinhibition and possibly related to clinical rigidity.

adults (Albin *et al.*, 1990; Louis *et al.*, 2000). Moreover, the classic hyperkinetic (choreic) state of Huntington's disease may often evolve towards an akinetic one (Bruyn and Went, 1986). Although we did not observe any differences between groups in the rigidity score from the UHDRS (Table 1), nor did we detect any difference in estimated number of years since first symptoms were noted or duration of the disease, it is possible that the largely non-choreic patients in our Huntington's disease-NCE group nevertheless constituted a rigid variant form of Huntington's disease. These data confirm earlier results we had obtained using a different form of the masked-prime task, showing that five out of 12 Huntington's disease patients evidenced an absent NCE (A. R. Aron, F. Schlaghecken, R. Barker, B. J. Sahakian and T. W. Robbins, unpublished observations). However, for that experiment, the greater chorea score for the disinhibited patients was not significantly different from that for the others.

Finally, we could not rule out the possibility that the disruption of the NCE for these patients may not have been due to a disturbance in some other component of the activation-followed-by-inhibition process consequent upon striatal damage. To explore this possibility, we used fMRI to investigate whether the response inhibition would localize to the striatum in healthy volunteers. Additionally, we planned to investigate the potential involvement of pallidal and thalamic structures in these processes, given their known role in connecting with cortico-striatal neural loops (Alexander *et al.*, 1990).

Experiment 2

Methods

We planned to identify brain regions specific to response-inhibition (as opposed to prime activation and response

conflict processes) by means of a dissociation analysis (Table 2). This relied on ANOVA (analysis of variance) and was based on an understanding of the different processes constituting activation-followed-by-inhibition from prior EEG results (Eimer and Schlaghecken, 1998) (Fig. 2).

In this experiment, neutral trials were included as a baseline condition. Computing contrasts between neutral trials and (compatible and incompatible) prime trials had the advantage of eliminating activity related to overt left-hand and right-hand responses, thereby leaving only those activity patterns reflecting processes triggered by the primes. As outlined in the Introduction, response-inhibition will only be triggered after the initial prime activation phase, and presenting a target immediately after the prime will thus cut off the response inhibition process. Consequently, the present experiment employed two prime-target ISI conditions, one long (150 ms), allowing response inhibition to take place, and one short (0 ms), preventing response inhibition from developing.

Table 2 indicates how the three processes of interest may be isolated by performing ANOVA on the values for brain regions activated by the four contrast conditions (C150-N150, I150-N150, C0-N0, I0-N0). In each case, a particular process requires a distinct pattern of activation of a brain region across the four conditions. The prime-activation process may be assessed by testing whether the mean of the four conditions is significantly different from zero; the response inhibition process is assessed by testing the main effect of ISI (150 versus 0); and response conflict is assessed by testing the interaction between ISI and compatibility. We tested these effects using ANOVA based on the average activation of defined regions of interest (ROIs). Although this method allowed resolution only at the level of different anatomically defined brain structures, it was statistically more rigorous than attempting to analyse the data voxel by voxel.

Participants

Twelve healthy paid volunteers participated in the scanning experiment (four male, mean age 27.3 ± 3.6 years, SD). An additional group of seven subjects (three male, mean age 31.0 ± 4.1 years) participated in the forced choice trials (under identical conditions with the exception that the scanner was not running during the task). According to self-report, all participants were right-handed and had normal or corrected-to-normal vision. Participants provided written informed consent, and were screened to ensure they satisfied MRI safety requirements and had no history of neurological or psychiatric illness. The study was approved by the Cambridgeshire Health Authority Local Research Ethics Committee.

Task

Stimulus presentation and response collection for healthy subjects in the scanner were similar to those for the Huntington's disease patients outside the scanner (see Experiment 1, Methods) with the exceptions that (i) stimuli subtended a visual angle of approximately $4^\circ \times 3^\circ$, (ii) stimuli were presented by a computer-controlled mirror projection system, and (iii) responses were collected with an MR-compatible button-box. The experimental procedure, however, was somewhat different. As outlined above, there were now two ISI conditions (150 and 0 ms) and additional neutral trials (lacking directional primes) were introduced. The ISI=0 condition would allow comparison of inhibitory with non-inhibitory events [when ISI = 0 ms, there is no time for inhibition to operate (Schlaghecken and Eimer, 2002)].

In ISI=0 blocks, targets appeared together with the mask (0 ms ISI after the prime). In ISI=150 blocks, targets appeared 50 ms after offset of the mask (150 ms ISI after the prime). Trial duration was thus 1010 ms in ISI=0 blocks and 1160 ms in ISI=150 blocks. The intertrial interval was varied randomly in 500 ms steps between 2000 and 4000 ms, thus jittering the stimuli with respect to imaging acquisition.

Each participant performed four experimental blocks of 60 trials each, two for each ISI condition. The order of blocks was counterbalanced across participants. Before scanning, participants practised the task (one block of 20 trials for each ISI condition).

For the forced choice test, subjects performed 10 practice trials, then 100 trials of which 80% used 32 ms primes, 10% 64 ms primes and 10% 96 ms primes. There were no targets on trials and subjects had to do their best to guess the direction of the prime on each trial.

Behavioural data analysis

Repeated measures ANOVAs were performed on reaction times for the factors prime-target ISI (0 ms, 150 ms) and compatibility (compatible, neutral, incompatible). Simple effects analyses were performed to assess the difference

between compatible and incompatible trials at each ISI. Because overall number of errors was small (fewer than four per type on average), no statistical analysis of error rates was conducted. For the forced choice trials for the 32 ms primes alone, a *t*-test was performed on the difference between the percentages of correct and incorrect responses.

Imaging and image processing

For scanning we used a MedSpec (Bruker, Ettlingen, Germany) at 3 T. We acquired fMRI volumes as 21 slices of 5 mm using gradient-echo echoplanar imaging (EPI) [TR/TE (repetition time/echo time) 3000/20 ms, flip angle 90° , matrix 128×128 , bandwidth 200 kHz]. For each experimental block, 100 EPI T_2^* -weighted whole-brain images in the axial plane were acquired. The first six EPI images of each block, acquired before stimulus presentation, were discarded to avoid T_1 calibration effects.

For each participant, a slice-timing correction compensated for the staggered order of slices acquired by EPI. Scans for each block were realigned to the first image of that block, and each session was realigned to the first image of the first block, in order to correct for head motion. A mean functional image volume was constructed for each participant from the realigned image volumes. Each volume was examined using MRICro (Rorden and Brett, 2000), and areas of signal dropout (especially temporal areas and orbitofrontal cortex) were masked. Images were spatially normalized to the standard Talairach reference frame by matching each masked image volume to a standardized template from the Montreal Neurological Institute (MNI) and employing linear and non-linear 3D transformations. The resultant functional images were spatially smoothed to accommodate inter-subject differences in anatomy, using isotropic Gaussian kernels of 8 mm. Low-frequency noise was removed using a high-pass filter (to a maximum of 1/120 Hz).

The haemodynamic responses evoked on each trial were modelled as single events convolved with a canonical haemodynamic response function using the general linear model as implemented in SPM99 (statistical parametric mapping software; Institute of Neurology, London, UK). Modelling of different event types was time-locked to prime onset on each trial. For each participant, a model was fitted which included all event types in both the ISI=150 and the ISI=0 condition. Incorrectly executed trials were excluded from analysis. We covaried for reaction time in a condition-specific manner to increase power to detect differences between events by reducing error variance. This increase in power was borne out by an exploratory analysis.

In accordance with our psychological model of the prime activation, response-inhibition and response conflict processes (Table 2), the following contrast images were generated for each subject: (i) C150-N150; (ii) I150-N150; (iii) C0-N0; (iv) I0-N0. This yielded a total of 48 contrast images. In each case, subtracting the baseline neutral event (on which there was no directional prime stimulus) led to the removal of

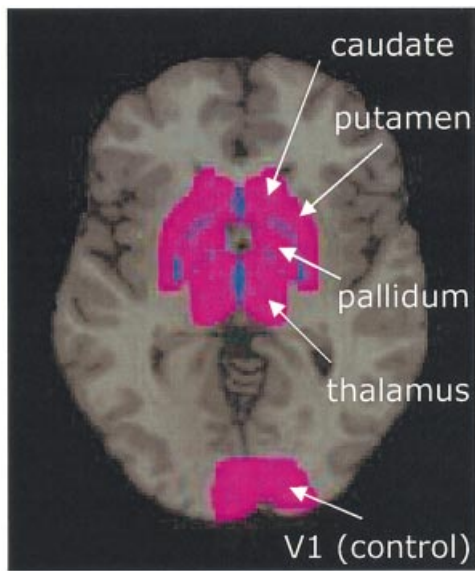


Fig. 4 Regions of interest (ROIs) are shown overlaid on a single axial slice, through the basal ganglia, of the structural template image from SPM96. These five separate ROIs form the basis for the analysis of functional imaging data from the healthy volunteers performing the masked priming task.

all potentially confounding perceptual, selective or motor processes. The remaining activation differences in the voxels would be due uniquely to our component psychological processes of interest.

ROI

ROIs were defined as the caudate, putamen, thalamus and pallidum, and a control ROI of roughly the same volume (Fig. 4). The control ROI consisted of ventral V1 of the occipital cortex, which is unlikely to play any role in the processes under study here. ROIs were derived from the Automated Anatomical Labeling template map (Tzourio-Mazoyer *et al.*, 2002). The ROIs were then transformed into the same voxel dimensions as the EPI template image from SPM99 and therefore that of the 48 contrast images acquired above. The average voxel activation for each contrast image was then computed for a particular ROI by summing the values of the voxels in the ROI and dividing this sum by the number of voxels in the ROI. This procedure was repeated for all contrast images and all ROIs. The output values were then exported to SPSS software (SPSS Inc., Chicago, IL, USA) for ANOVA. Exploratory data analysis indicated that the average signal change values for one subject were extreme and this subject was removed from further image-related analysis.

Results

Behavioural results

Relative to neutral trials, reaction times were longer on incompatible trials and shorter on compatible trials in the

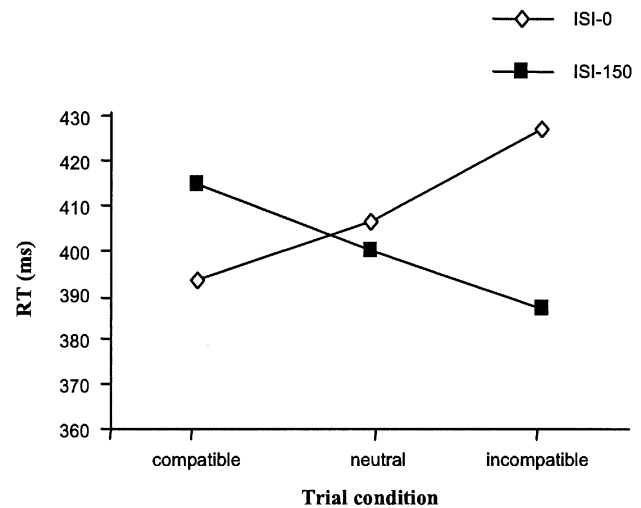


Fig. 5 Behavioural data acquired during fMRI scanning. Correct mean reaction times are shown for each condition. The data replicate the classic masked priming effect showing faster reaction time (RT) for compatible than for incompatible trials (the positive compatibility effect, PCE) when the prime–target interval is 0 ms, and the reverse, negative compatibility effect (NCE) when the interval is 150 ms.

ISI–0 condition, while the reverse was true in the ISI–150 condition (Fig. 5) [interaction ISI \times compatibility, $F(2,22) = 48.0$, $P < 0.001$]. Simple effects analyses confirmed the usual PCE with short ISI [$t(11) = -5.5$, $P < 0.001$] and NCE with long ISI [$t(11) = 4.4$, $P < 0.001$]. Error rates (not statistically analysed) showed a similar pattern. Therefore, the behavioural result in the scanner mimicked the standard masked-prime effect seen outside the scanner (Schlaghecken and Eimer, 1997; Eimer and Schlaghecken, 1998, 2001; Schlaghecken *et al.*, 2001), and we could be confident in exercising the psychological components of interest to a maximum.

We confirmed that the prime stimuli were subliminal by testing seven additional subjects on forced choice trials in the scanner. Participants correctly identified a 32 ms prime on 54% of all trials and made an incorrect response on 46%. A paired t -test showed that this result was not significantly different from chance performance [$t(6) = 0.9$].

fMRI results

Figure 6 summarizes the results of the imaging analysis and should be carefully compared with Table 2. For each ROI the pattern of average signal change for each condition is plotted. It is evident that neither the pattern for prime activation nor the pattern for response conflict emerge for any ROI [this is borne out by non-significant statistical tests for the mean of the conditions ($F < 1$ for all ROIs) and the interaction between ISI and compatibility ($F < 1$)]. By contrast, the pattern expected for response–inhibition (main effect of ISI) is evident, and this was a significant effect for the caudate [$F(1,10) = 5.1$, $P < 0.05$] and for the thalamus [$F(1,10) = 20.0$,

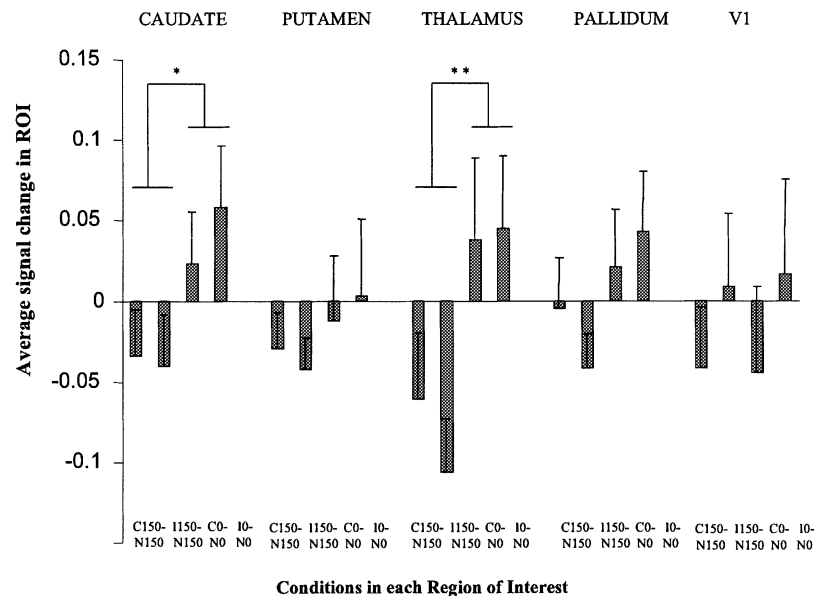


Fig. 6 Average signal change over regions of interest (ROIs) related to prime activation, response inhibition and response conflict. The caudate ($*P = 0.03$) and thalamus ($**P = 0.001$) show a statistically significant effect of response inhibition, but the putamen and pallidum do not ($F < 1$). Moreover, prime activation and response conflict do not engage any of the ROIs ($F < 1$). Response inhibition is indicated by a main effect of ISI, i.e. inhibition occurs when ISI = 150 ms (C150–N150 and I150–N150 contrasts) but not when ISI = 0 ms (C0–N0 and I0–N0 contrasts). Average signal change is computed for each of these contrasts for each ROI by summing the values of each voxel in the ROI and dividing by the number of voxels in the ROI.

Table 2 Logic of statistical analysis showing the pattern expected at a particular ROI for each of several postulated psychological processes

	C150–N150	I150–N150	C0–N0	I0–N0
Prime activation	Yes	Yes	Yes	Yes
Inhibition	Yes	Yes	–	–
Response conflict	Yes	–	–	Yes

C150–N150, for example, denotes the contrast of compatible trials and incompatible trials with prime–target interval of 150 ms. For this particular contrast, an ROI (e.g. average signal change for entire caudate) could be ‘activated’ or ‘deactivated’ (denoted by ‘Yes’) by any of the three processes (see below). In *prime activation*, a masked prime triggers partial activation of its corresponding motor response. The activation process is independent of prime–target ISI, and only requires that a response has been assigned to the prime. On neutral trials, where the prime is not assigned to any response, no prime activation occurs. In *response inhibition*, provided a response is assigned to the prime and the interval between prime and target is long enough, initial prime activation will be inhibited and the opposite response will be relatively more activated. If target-related response processes start during this phase, behavioural benefits will be found for incompatible trials, and behavioural costs will be found for compatible trials (NCE). Consequently, inhibition indexes an ROI that shows a difference between compatible and neutral trials and between incompatible and neutral trials in the ISI–150 condition but not the ISI–0 condition. *Response conflict* occurs when the representation required by the target is currently subject to inhibition (C150–N150) or when the opposite response is currently active (I0–N0).

$P < 0.001$], but not for the putamen [$F(1,10) < 1$], pallidum [$F(1,10) = 4.0$] or control area V1 [$F(1,10) < 1$]. The test of the main effect of ISI is appropriate because, as is made clear in Table 2, response inhibition indexes an ROI that shows a difference between compatible and neutral trials and between incompatible and neutral trials in the ISI–150 condition but not the ISI–0 condition. As behavioural and electrophysiological data suggest that response inhibition does not occur in the ISI–0 condition, the ISI–0 condition constitutes the baseline from which to compare the ISI–150 inhibitory condition. The main effect of ISI assesses this difference and shows that both the caudate and the thalamus ROIs contain regions, or substructures, which are significantly modulated by the process of response inhibition. Finally, as the expected number of false-positive tests equals the number of tests (5 regions multiplied by 3 contrasts) multiplied by the α value ($P = 0.05$), we computed the expected number of false positives to be 0.75. Therefore, as the expected number of false-positive tests was less than one, we concluded there was little need for a conservative correction of the α value.

Discussion

Previous research has shown that masked primes trigger an initial activation of their corresponding response, which is later subject to inhibition (Klotz and Wolff, 1995; Schlaghecken and Eimer, 1997; Dehaene *et al.*, 1998;

Eimer and Schlaghecken, 1998; Eimer, 1999). At the behavioural level, this pattern of activation-followed-by-inhibition results in an NCE, with behavioural costs on compatible trials and benefits on incompatible trials. Electrophysiological data (Fig. 2) have revealed the time course of the motor processes underlying the NCE. On the basis of a prior repetitive transcranial magnetic stimulation study (Schlaghecken *et al.*, 2001) we hypothesized that these processes would implicate the striatum. In the present study, evidence in favour of this hypothesis was obtained. First, it was shown that some Huntington's disease patients had PCEs instead of NCEs, these being the patients with the greatest chorea (a 'disinhibition' syndrome), while the remainder of patients showed significantly greater NCEs than the control group. Secondly, fMRI on healthy participants indicated a specific role for the caudate nucleus in response inhibition.

In order to isolate brain areas specifically involved in this subprocess, a dissociation logic based on the activation-followed-by-inhibition account of masked priming was applied. According to this account, inhibition is elicited both on compatible and incompatible trials, but only when prime-target ISIs are sufficiently long. By contrast, signal change due to primed responses would be triggered on all prime trials, independently of prime-target ISI. Signal change triggered by a response conflict between the response required by the target and the response preactivated by prime activation and/or inhibition processes would be restricted to compatible trials at long ISIs and incompatible trials at short ISIs. By restricting the analysis to those brain areas (ROIs) that showed signal change selectively corresponding to one of these patterns, we were able to separate the response inhibition process from prime activation or response inhibition despite the fact that they occur within a single trial on a millisecond time scale.

Following this dissociation approach, the present data indicate that both the caudate and the thalamus are specifically involved in response inhibition. Moreover, since we verified that the directional primes were subliminal, we showed that the caudate and thalamus may be implicated even when such response inhibition operates on subliminally generated movements. This suggests a revision to an influential hypothesis of basal ganglia function, depending largely on single-neuron electrophysiological recordings in non-human primates, which states that the basal ganglia inhibit competing motor tendencies to prevent interference with purely voluntary action (Mink, 1996). The present finding that the inhibition of primed response tendencies involves caudate and thalamus ROIs provides human data in support of this model, but suggests it should be extended to include not only the inhibitory control of voluntary movements but also the inhibition of involuntary, subliminally triggered movements.

Inspection of Fig. 6 indicates that there were 'deactivations' for compatible ISI-150 and incompatible ISI-150 events relative to neutral events, whereas this was not the case for the ISI-0 condition. Therefore, this is not simply a case of

the phenomenon of repetition suppression, in which a decrease in brain activity is observed when a subject is exposed first to a prime and then to a target stimulus (e.g. Schacter and Buckner, 1998; Wiggs and Martin, 1998), since the ISI-0 condition also involved primes (e.g. C0-N0). Although deactivations can sometimes be difficult to interpret (Gusnard and Raichle, 2001), the pattern of deactivations shown here for the caudate and thalamus is consistent with a plausible model of how the striatum interacts with cortical function if one assumes that 'deactivation' in fact reflects reduced neural activity within the caudate. Thus, response inhibition may be manifested in reduced striatal activity (perhaps due to reduced input, or even to increased input leading to greater suppression of caudate activity by inhibitory interneurons) leading to less inhibition of the *medial* globus pallidus and therefore more thalamocortical suppression via the direct pathway of the basal ganglia (Beiser *et al.*, 1997). Our finding, in healthy volunteers, of significant deactivation in both caudate and thalamus for inhibitory versus non-inhibitory psychological events is consistent with the operation of this direct pathway.

Efficient inhibitory control of this type probably requires a balance of input into the pallidum of both direct and indirect pathways, the relative timing of which is crucial (for an account based on neurophysiological recordings see Mink, 1996). A common theory of movement disorders maintains that chorea results from preferential loss of striatal neurons projecting to the *lateral* globus pallidus (leading to over-excitation of thalamocortical motor output), while rigid-akinetic Huntington's disease and bradykinesia are a consequence of the additional loss of striatal projections to the *medial* globus pallidus [leading to underactivation of thalamocortical motor output (Albin *et al.*, 1990)]. Our finding that the Huntington's disease-PCE group of patients, with abolished response inhibition, had significantly greater chorea than Huntington's disease-NCE patients is consistent with the model of preferential striatal loss to the lateral globus pallidus. By contrast, the exaggeration of the NCE in the Huntington's disease-NCE group may, we speculate, have resulted from the presence of some members in this group with symptoms of the rigid-akinetic or bradykinetic type. While we have limited evidence that this task is capable of distinguishing different varieties of Huntington's disease, more conclusive findings would have clinical implications for deciding among neuropharmacological treatment options and assessing remedial treatment strategies.

Moreover, the present findings motivate the exploration of the time course of the activation-followed-by-inhibition process using event-related potential recordings of Huntington's disease patients performing the masked-priming task, as well as potential fMRI investigations focused explicitly on substructures of the basal ganglia and on revealing the cortical source of the inhibitory signal. Additionally, we are investigating the behavioural profile of Parkinson's disease patients with this task.

This study has shown how it is possible to image the neural processes by which perceptual information acts directly on the motor system (Neumann and Klotz, 1994), even when such processes operate within a brief 300 ms interval well below the temporal resolution of fMRI. In particular, we have isolated the inhibitory process that operates on such response dispositions, even when they are subliminal, and have shown that it implicates the caudate nucleus and the thalamus. The findings are consistent with current understanding of the direct and indirect pathways of the basal ganglia: healthy controls implement response inhibition via the normal operation of the direct pathway, and choreic Huntington's disease patients show disinhibition because damage to the indirect pathway leads to overexcitation of thalamocortical output. The inhibitory process studied here was elicited by means of a behavioural priming paradigm, increasingly a method of choice in fMRI (Naccache and Dehaene, 2001) and one allowing the inhibitory process to be turned on or off by manipulating a single parameter. This task may constitute a fruitful tool for further investigations of the motor system and the sensitive assessment of remedial treatments for basal ganglia disorders.

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