

# Single subthalamic nucleus deep brain stimuli inhibit the blink reflex in Parkinson's disease patients

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**The disordered output from the basal ganglia to the pontine tegmentum nuclei is considered responsible for a number of abnormalities in brainstem reflexes in patients with Parkinson's disease. One of the most conspicuous of these abnormalities is the reduced inhibition of the blink reflex by a prepulse stimulus. The circuit of prepulse inhibition involves structures and fibre groups that can be reached by stimuli applied through the electrodes implanted in the subthalamic nucleus for deep brain stimulation (STNDBS). In seven Parkinson's disease patients we examined whether single STNDBS induced prepulse effects on the blink reflex and how they compared with the effects induced by single auditory and somatosensory stimuli. Prepulse inhibition was determined by measuring the percentage inhibition induced in the R2 component of the orbicularis oculi response to supraorbital nerve stimuli. The inter-stimuli intervals (ISI) between the prepulse and the supraorbital nerve stimuli were 0 to 30 ms and 100 ms for single STNDBS and 100 ms for auditory and somatosensory modalities. The results obtained with acoustic and somatosensory stimuli were compared with those obtained from a group of 20 age-matched healthy subjects. Single STNDBS induced significant inhibition of the R2 in all patients at ISIs between 10 and 30 ms, with a mean percentage inhibition of 94% at the ISI of 30 ms. On the contrary, significant inhibition by auditory or somatosensory stimuli was induced in only two out of the seven patients. The mean percentage inhibition at the ISI of 100 ms was 37% for auditory and 40% for somatosensory stimuli, well below reference limits for prepulse inhibition in control subjects (61%). Single STNDBS induces significant prepulse inhibition of the blink reflex in Parkinson's disease patients who have abnormally reduced auditory and somatosensory prepulse effects. This finding helps define the prepulse circuit in humans and the eventual site of its dysfunction in Parkinson's disease.**

**Keywords:** subthalamic nucleus; deep brain stimulation; prepulse inhibition; blink reflex; Parkinson's disease

**Abbreviations:** DBS = deep brain stimulation; GPi = globus pallidus internus; ISI = inter-stimulus interval; nRPC = nucleus reticularis pontis caudalis; OOc = orbicularis oculi; PPTg = pedunculo-pontine tegmental nucleus; SNr = substantia nigra pars reticulata; STN = subthalamic nucleus; STNDBS = subthalamic nucleus deep brain stimulation.

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## Introduction

The effects induced by a stimulus so weak that is unable to induce any response by itself on the response to another stimulus are known as prepulse effects (Graham, 1975; Hoffmann and Ison, 1980; Ison *et al.*, 1990; Blumenthal, 1999; Valls-Solé *et al.*, 1999). Prepulse inhibition of the blink reflex has been reported to be abnormally reduced in Parkinson's disease, as well as in other neurological disorders (Nakashima *et al.*, 1993; Schicatano *et al.*, 2000; Valls-Solé *et al.*, 2004). From the available literature on animal

experimentation it is known that the pedunculo-pontine tegmental nucleus (PPTg), the nucleus reticularis pontis caudalis (nRPC) and the substantia nigra pars reticulata (SNr) are crucial structures involved in the circuit of prepulse inhibition (Fendt *et al.*, 2001; Swerdlow *et al.*, 2001). The basal ganglia are likely to exert their control over the prepulse circuit through the PPTg, which has reciprocal connections with multiple nuclei, including the subthalamic nucleus (STN), the globus pallidus internus (GPi) and the SNr

(Garcia-Rill, 1991; Inglis and Winn, 1995; Reese *et al.*, 1995; Kretschmer and Koch, 1998).

High-frequency deep brain stimulation (DBS) is a procedure widely used to improve motor symptoms in patients with advanced Parkinson's disease. Apart from the therapeutic potential of the technique, the presence of electrodes implanted in deep brain tissue provides a unique opportunity to study in humans neurophysiological features of structures and neural circuits situated within the area of influence of the stimulus. With this purpose, DBS electrodes have been used by several authors for stimulation or recording (Strafella *et al.*, 1997; Ashby *et al.*, 1999; Baker *et al.*, 2002; Kuhn *et al.*, 2004). The hypothesized circuits mediating prepulse effects are likely to be affected by electrical stimuli applied through the electrodes used for DBS. Therefore, in order to improve our knowledge on the circuits of prepulse inhibition in humans, we investigated whether a single intracerebral electrical stimulus applied through the microelectrodes inserted in the STN for DBS purposes (sSTNDBS) induced prepulse effects on the blink reflex and how these effects compared with those induced by auditory and somatosensory stimuli.

## Patients

We studied seven patients with advanced Parkinson's disease after neurophysiologically guided stereotactic surgery for implantation of DBS electrodes in the STN. Electrode location in the target was verified using postoperative MRI scans. Patients were four males and three females, with a mean age of  $54 \pm 12$  years (range: 41–70 years). Their mean Hoehn and Yahr OFF stage was  $3.3 \pm 0.5$  (range: 3–4) and their mean disease duration was  $21 \pm 13$  years (range: 12–45). One patient was parkin positive. The electrodes for long-term stimulation (Medtronic, 3389; Minnesota, USA) were left externalized for up to 3 days before programmable pulse generators were implanted in the subclavicular area. The externalized electrodes were accessible to controlled neurophysiological interventions (*see below*) using an adapted Medtronic switch connecting all four leads to terminals suitable for the stimulator of an electromyograph (Mystro5Plus, Oxford Instruments, Surrey, UK). Patients were all examined in overnight 'off medication' condition. All patients gave their written informed consent for the study, which was approved by the Ethics Committee of the Hospital Clinic of Barcelona.

## Methods

### Recording

Patients were lying in the examination bed, relaxed, in a dimly lit room. They were instructed not to speak and to remain calm and relaxed during the experiment. All neurophysiological studies were performed by the same examiner, under the same experimental conditions and with the same equipment. The EMG activity of the orbicularis oculi (OOc) muscle was recorded by means of surface silver/silver chloride 9-mm-diameter recording electrodes

attached to the skin overlying the lower part of the right OOc muscle, the active electrode in the middle portion of the muscle and the reference electrode 3 cm lateral to it.

### Stimulation

All stimuli were delivered through the stimulator system of the electromyograph.

We elicited the blink reflex to supraorbital nerve stimuli using conventional procedures (Kimura, 2001). Supraorbital nerve stimuli were applied with surface electrodes, the cathode over the supraorbital notch and the anode 3 cm away over the course of the nerve in the ipsilateral forehead. The R1 and R2 responses were identified as those action potentials of similar shape recorded in successive stimuli at the expected onset latency. The stimulus intensity and exact position of the stimulating electrodes were chosen to elicit a stable artefact-free R2 response.

For sSTNDBS, we used bipolar stimulation montages between the two extreme electrode leads (the most caudal one, electrode-lead 0, and the most rostral one, electrode-lead 3). The DBS electrodes used in our patients have four platinum–iridium contact poles separated by 2.0 mm, each pole measuring 1.50 mm in length and 1.27 mm in width. Therefore, the assumed distance between cathode and anode in our montage was 7.5 mm. Electrode-lead 0 was used as cathode. Stimuli were of 0.2 ms duration. We used a stimulus intensity that did not induce any response in the OOc. However, in order to be sure that we were activating structures with motor effects (Valls-Solé *et al.*, 2000), we determined the threshold intensity for eliciting motor responses in the OOc of either side. This was defined as the minimum stimulus intensity in milliamperes that induced responses with amplitude of at least 0.1 mV. The prepulse stimulus intensity used during the experiment was 90% threshold.

The same electromyograph was used to trigger acoustic and somatosensory prepulse stimuli. The acoustic prepulse stimulus was a sound generated by discharging the coil of a magnetic stimulator (MagStim 200; Whitland, Dyfed, UK), hanging freely in the air at a distance of  $\sim 1$  m from the subject's head, following a previously described protocol (Valls-Solé *et al.*, 1999). The intensity of the sound was regulated by changing the intensity of the magnetic stimulus and accurately measured with a Brüel and Kjaer impulse precision sound level meter type 2204 and a condenser microphone cartridge type 4145. We used an intensity of 70 dB (SPL). Background noise level was kept below 50 dB, the upper limit for the perceived noise level accepted in our hospital wards. The somatosensory prepulse stimulus was a weak electrical shock, of an intensity around 1.5 times the individual's sensory perception threshold, delivered through a pair of ring electrodes attached to the third finger. The intensities of both prepulse stimuli used did not elicit any response in OOc.

### General procedure

We began data collection after individually adjusting the intensities for the supraorbital nerve stimuli. Stimulator A of the EMG triggered the prepulse stimuli (the sSTNDBS, the acoustic or the somatosensory stimulus), while stimulator B triggered the response-eliciting stimulus, which was always the supraorbital nerve electrical stimulus. We applied pairs of control and test trials, all intermingled in random order, with at least 30 s between two consecutive trials. Control trials were those containing only the response-eliciting

stimulus. Test trials were those containing the same stimulus preceded by the prepulse stimulus. Alternation between control and test trials was done five times for each inter-stimuli interval (ISI) and stimulus modality.

### Assessment of prepulse effects

The ISIs chosen to explore the sSTNDBS effects were 0, 5, 10, 15, 20, 25, 30 and 100 ms. The shorter ISIs (0–30 ms) were selected because of the likelihood of shorter latency effects of sSTNDBS in comparison with acoustic and somatosensory stimuli, and because significant inhibition was shown in animal models at these ISIs (Li and Yeomans, 2000). We performed the experiments on the sSTNDBS prepulse by using the DBS electrode on the right side in four patients, and the one on the left side in three patients. In all cases, the supraorbital nerve stimulus was applied in the ipsilateral side of the sSTNDBS prepulse. Additionally, in one patient we looked at the effects of ipsi- and contralateral sSTNDBS stimulation on the blink reflex.

The assessment of prepulse inhibition by acoustic and somatosensory stimuli was performed together with the assessment of sSTNDBS effects. The ISI chosen was 100 ms because this was the ISI showing the most abnormal decrease in prepulse inhibition in previous works done in Parkinson's disease patients (Nakashima et al., 1993; Valls-Solé et al., 2004).

### Data reduction and analysis

All recordings were printed on paper and analysed off-line independently by two of the authors (J.C. and C.P.). The mean values obtained from these two measurements were used for statistical analysis. We measured the latency and amplitude of R1 and latency and area (amplitude times duration) of R2 and R2c in all control and test trials at every ISI. For each prepulse modality we assigned the value of 100% to the mean calculated for each one of the above parameters measured in control trials. We expressed the mean values calculated for the same parameters in test trials as the difference in percentage from 100% in absolute values [i.e.  $100 - (R2 \text{ test}/R2 \text{ control}) \times 100$ ]. When responses were absent, they were not taken into account for calculation of the mean latency, and were given the value of 0 for calculation of the mean amplitude. Group results are expressed as mean  $\pm$  standard deviation.

We analysed sSTNDBS results by grouping all data on the same ISI from all patients. Statistical analyses were done with repeated-measures one-factor ANOVA (analysis of variance) to determine the effects of ISI as independent variable on the latency and size of R1, R2 and R2c responses. Tukey *post hoc* test was used to explore

the nature of significant effects found in ANOVA. We also determined whether there were changes induced by the prepulse in data from single individuals. Because of the lack of normative data with DBS, we arbitrarily defined that a response was facilitated or inhibited if there was a change of >20% of the mean value of the responses obtained in the corresponding control trials in the latency of R1 or R2, the amplitude of R1 or the size of R2. We then calculated the relative frequencies of facilitated and inhibited responses in test trials across all ISIs for each individual. Since we performed 5 tests trials for each one of the 8 ISIs studied and for each patient ( $n = 7$ ), a total of 280 responses were available for analysis ( $5 \times 8 \times 7$ ).

We analysed acoustic and somatosensory results by comparing the mean changes in the R1, R2 and R2c responses obtained in control trials and test trials for each prepulse modality at an ISI of 100 ms (one-factor ANOVA). In addition, the mean prepulse inhibition of the R2 and R2c responses caused by acoustic and somatosensory stimuli in patients was compared with that obtained in a control group of 20 healthy volunteers matched for age and sex, examined in the same department by the same person and with the same technique (Valls-Solé et al., 2004). Group analyses were done by comparing the data obtained at the ISI of 100 ms in control subjects and patients for each prepulse modality (one-factor ANOVA). We also carried out an analysis of individual data by using the reference limits for normal prepulse inhibition (mean + 2.5 SD), calculated from the study done in the control group of healthy subjects (Valls-Solé et al., 2004). For the ISI of 100 ms the upper limit was 61.35% inhibition for somatosensory prepulse, and 63.55% inhibition for acoustic prepulse.

All statistical analyses were done using SPSS 13.0 for Windows. The level of significance was set at  $P = 0.05$ .

### Results

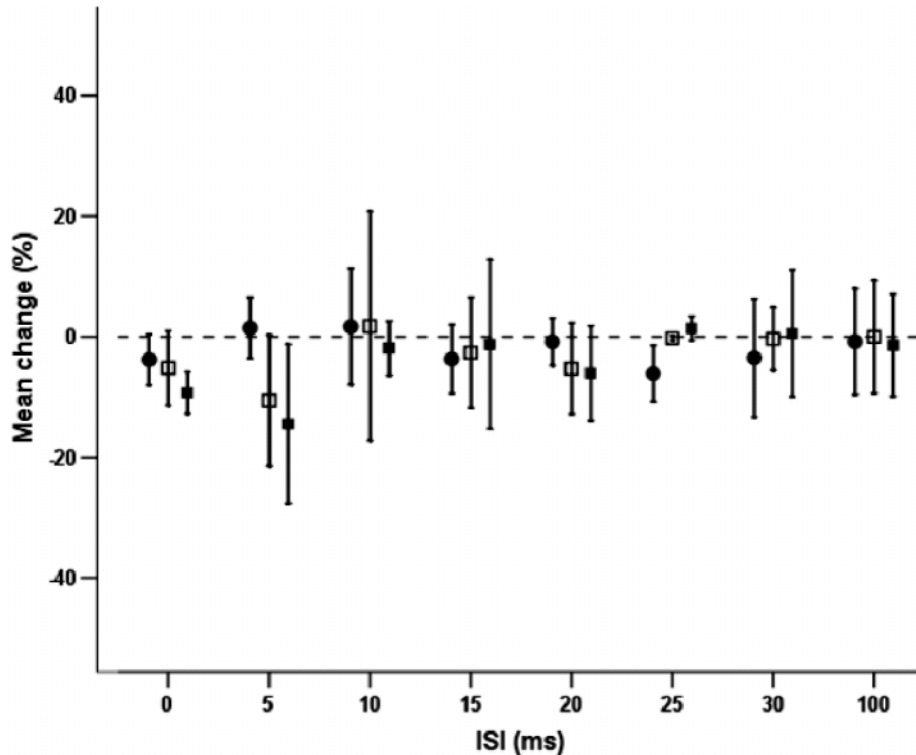
No patient reported any pain or discomfort during or after the experiments, except for the mild discomfort derived from supraorbital nerve electrical stimulation. Specifically, no patient reported noticing the sSTNDBS at the intensities used in the study. Occasional higher-intensity sSTNDBS delivered while assessing the individual's threshold intensity caused a twitching in facial and upper limb muscles.

Mean values of OOC responses to trigeminal nerve stimulation in control and selected test trials are presented in Table 1.

**Table 1** Mean values in control trials of OOC responses to trigeminal nerve stimulation in Parkinson's disease patients

PD patients	R1 lat (ms)	R2 lat (ms)	R2c lat (ms)	R1 amp ( $\mu\text{V}$ )	R2 amp ( $\mu\text{V}$ )	R2c amp ( $\mu\text{V}$ )	R2 size (mV*ms)	R2c size (mV*ms)
Control trials	11.1 $\pm$ 1.2	39.3 $\pm$ 4.6	42.1 $\pm$ 5.8	173.6 $\pm$ 82.5	288.0 $\pm$ 139.1	192 $\pm$ 97.8	14.8 $\pm$ 6.8	8.2 $\pm$ 5.7
sSTNDBS (ISI: 30 ms)	-3.4 $\pm$ 9.8	-0.3 $\pm$ 5.1	-0.5 $\pm$ 10.5	27.4 $\pm$ 39.3	-86.1 $\pm$ 16.6	-80.7 $\pm$ 23.3	-94.2 $\pm$ 5.9	-95.9 $\pm$ 6.0
Somatosensory prepulse	-0.4 $\pm$ 2.0	-11.5 $\pm$ 6.5	-12.3 $\pm$ 5.8	172.4 $\pm$ 153.7	-32.4 $\pm$ 22.2	-34.1 $\pm$ 19.3	-40.4 $\pm$ 24.4	-42.4 $\pm$ 25.6
Acoustic prepulse	-1.4 $\pm$ 3.2	-14.2 $\pm$ 5.6	-11.8 $\pm$ 4.1	-144.8 $\pm$ 166.2	-30.2 $\pm$ 19.8	-33.1 $\pm$ 20.4	-37.4 $\pm$ 25.8	-40.1 $\pm$ 26.7

The mean percentage of change in test trials with sSTNDBS, somatosensory and acoustic prepulses is shown below. Positive values represent facilitation and negative values inhibition of the responses. For sSTNDBS the values presented are those for the ISI of 30 ms, in which the most marked inhibition of R2 and R2c was seen. lat, latency; amp, amplitude. Values represent mean  $\pm$  standard deviation.



**Fig. 1** Mean change in the latency of R1, R2 and R2c responses in all ISIs tested with sSTNDBS, expressed in percentage from the respective mean in control trials. Legend: R1 latency—filled circles; R2 latency—open squares; R2c latency—filled squares. Bars represent mean  $\pm$  standard deviation.

### sSTNDBS prepulse modulation of the blink reflex

There were no significant differences between control and test trials regarding the mean latencies of R1 [ $F(8,54) = 0.8$ ;  $P = 0.6$ ], R2 [ $F(8,54) = 0.9$ ;  $P = 0.5$ ] and R2c [ $F(8,54) = 1.9$ ;  $P = 0.1$ ]. Figure 1 shows the mean and standard deviation values for all ISIs tested. In individual recordings, a change in latency beyond 20% of the mean in control trials occurred in none of the R1 responses, in 25 R2 responses (9%) and in 20 R2c responses (7%).

The amplitude of R1 increased in test trials in comparison with control trials (Fig. 2) although the percentage facilitation across all ISIs did not reach statistical significance [ $F(8,54) = 1.8$ ,  $P = 0.09$ ]. The size of R2 and R2c responses decreased significantly in test trials in comparison with control trials [ $F(8,54) = 12.3$ ,  $P < 0.0001$  for R2, and  $F(8,54) = 5.2$ ,  $P < 0.001$  for R2c]. *Post hoc* analysis showed significant differences with respect to control trials in the percentage inhibition of both R2 and R2c ( $P < 0.01$ ) at ISIs between 10 and 30 ms (Fig. 2). There were no differences in the percentage decrease between R2 and R2c in any of the ISIs ( $P > 0.4$  for all comparisons).

The number of individual R1 and R2 responses considered to show significant changes (i.e. larger than 20% of the mean amplitude in control trials) is summarized in Fig. 3, as percentage of the total number of responses analysed in test

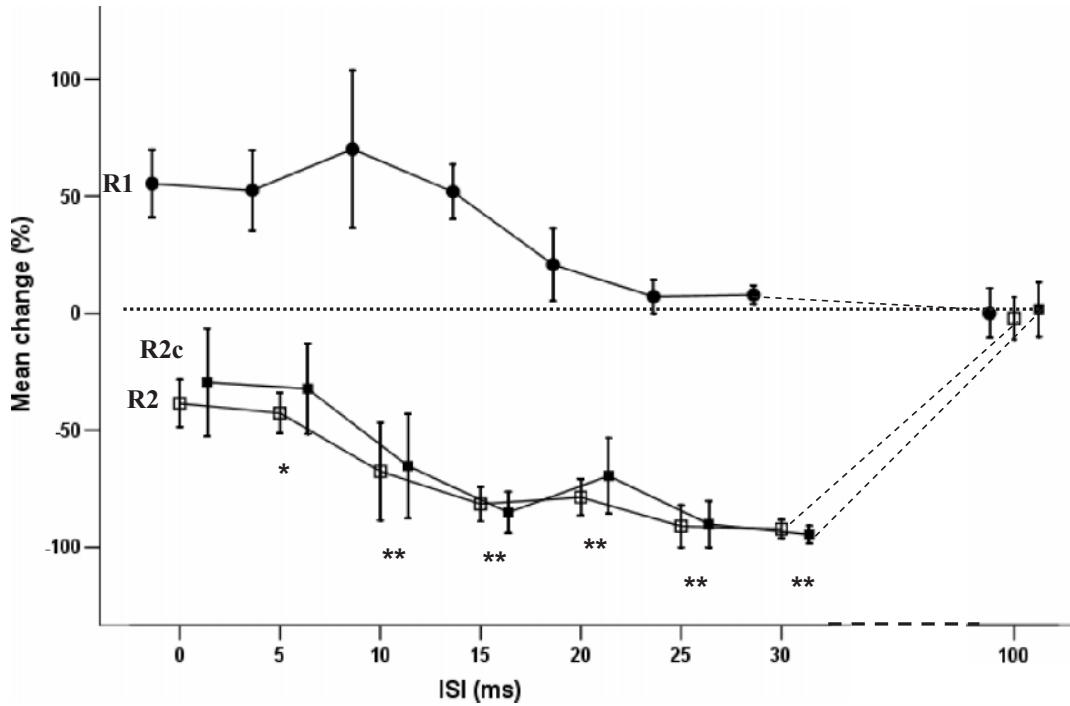
trials across ISIs. To avoid complexity, only the change in R2 is represented because of the similar findings in R2c.

No differences were observed in the mean latency, amplitude or size of responses elicited by either right- or left-side stimulation (unpaired *t*-test;  $P > 0.05$  for all comparisons). There were also no differences between ipsilateral and contralateral sSTNDBS in the data obtained from one patient (paired *t*-test;  $P > 0.05$ ). Figure 4 shows representative examples of the recordings from one patient.

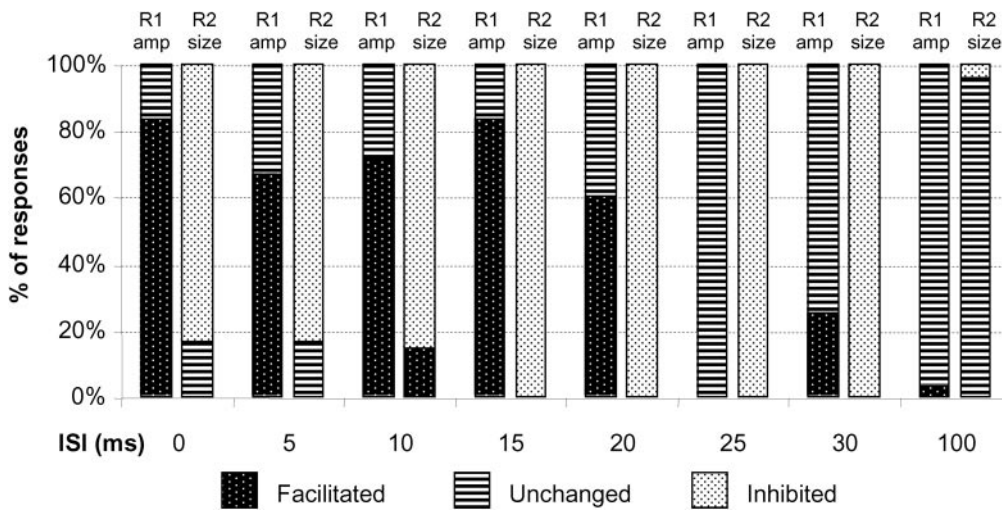
### Somatosensory and acoustic prepulse modulation of the blink reflex

The percentage of change in OOC responses is presented in Table 1. The latency of R1 was not different when comparing data from test acoustic, test somatosensory and control trials [ $F(2,25) = 0.78$ ;  $P = 0.47$ ]. The amplitude of R1 increased after both prepulse stimuli. However, it did not reach significance because of its high variability [ $F(2,25) = 3.2$ ;  $P = 0.06$ ]. The latencies of R2 [ $F(2,25) = 11.2$ ;  $P < 0.001$ ] and R2c [ $F(2,25) = 5.9$ ;  $P < 0.01$ ] were shorter in test trials than in control trials. *Post hoc* analysis showed that these differences were significant for both acoustic and somatosensory stimuli ( $P < 0.01$ ).

Compared with healthy controls, the inhibition of the R2 or R2c responses at an ISI of 100 ms was markedly reduced in patients. The mean percentage inhibition of R2 size with



**Fig. 2** Mean change in R1 amplitude, and R2 and R2c size in all ISIs tested with sSTNDBS, expressed in percentage from the respective mean in control trials. Legend: R1 amplitude—filled circles; R2 size—open squares; R2c size—filled squares. Bars represent mean  $\pm$  standard error. \* $P = 0.06$ ; \*\* $P < 0.01$  (in comparison with control). Note the significant percentage inhibition of the R2 and R2c responses at ISIs between 10 and 30 ms, and the percentage facilitation of the R1 response. There was no inhibition or facilitation of R1, R2 or R2c at 100 ms.

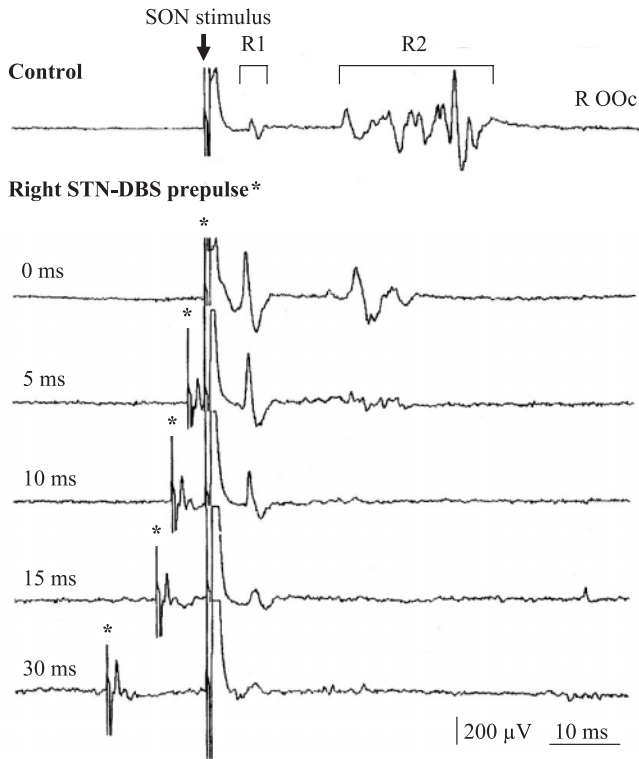


**Fig. 3** Relative frequency of the R1 and R2 responses showing significant facilitation (>120% of control), inhibition (<80% of control) or unchanged, in test trials at the ISIs explored. Note that none of the R1 responses showed inhibition and almost all of the R2 responses showed significant inhibition, at ISIs between 0 and 30 ms. At 100 ms almost none of the R2 responses showed inhibition.

somatosensory ( $40.4 \pm 24.4\%$ ) and acoustic ( $37.4 \pm 25.8\%$ ) prepulse in patients was significantly smaller than in healthy volunteers ( $94.9 \pm 5.2\%$  and  $91 \pm 6.2\%$ , respectively) [ $F(3,50) = 58$ ;  $P < 0.001$ ]. *Post hoc* analysis showed significant differences between controls and patients for both prepulse modalities ( $P < 0.001$ ). Within groups (controls and

patients) the inhibition of R2 to somatosensory and acoustic prepulse was similar. Similar percentages and levels of significance were gathered for R2c in both prepulse modalities.

Individually, five patients (71%) showed an abnormal reduction of the blink reflex to either somatosensory or acoustic prepulses, considering the upper limits obtained

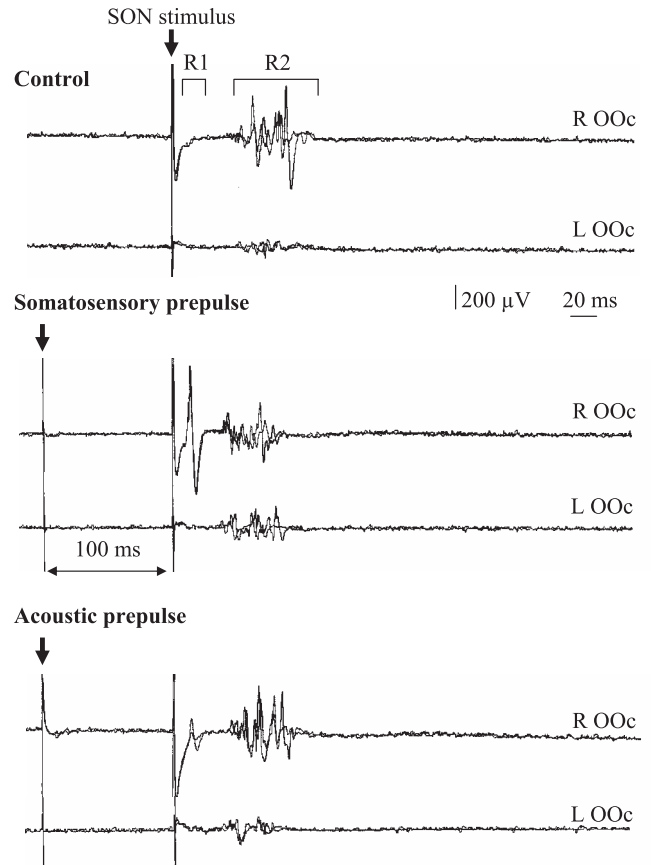


**Fig. 4** OOc responses to sSTNDBS prepulse in a representative case at ISIs between 0 and 30 ms. Legend: R OOc—right orbicularis oculi; SON—supraorbital nerve electrical stimulus. Note the increase in R1 amplitude from ISI 0 to 15 ms, and the decrease in R2 amplitude and size from ISI 0 to 30 ms.

in the control subjects. The other two patients had prepulse inhibition within normal limits in both somatosensory and acoustic prepulses. Figure 5 shows representative examples of the recordings taken from one of the patients with abnormally reduced prepulse inhibition.

## Discussion

The most relevant findings of our study are as follows: (i) sSTNDBS induces prepulse effects on the blink reflex, consisting of facilitation of the R1 and inhibition of the R2 and R2c. To our knowledge, this is the first time that prepulse effects are obtained with intracerebral stimulation in humans. The effect is more likely produced by stimulation of neighbouring tracts than the STN neurons themselves. However, the limitation of our study to patients with DBS electrodes implanted in the STN precludes any further speculation on whether stimulation through other nuclei would produce the same effect. (ii) The short latency of the facilitatory and inhibitory effects of sSTNDBS on the blink reflex indicates that they must be mediated by circuits in the vicinity of the STN. The dissociation between facilitatory and inhibitory effects on R1 and R2, respectively, as well as the absence of differences between R2 and R2c, suggests that the action of sSTNDBS should take place at



**Fig. 5** OOc responses to somatosensory and acoustic prepulses in a representative case. Legend: R OOc—right orbicularis oculi; L OOc—left orbicularis oculi; SON—supraorbital nerve electrical stimulus. Note the reduced R2 inhibition at an ISI of 100 ms.

a pre-motoneuronal level. (iii) The fact that somatosensory and acoustic prepulse inhibition of the blink reflex is reduced in the same patients in whom we found an effective inhibition using STN-DBS suggests that the mechanisms and brain structures conveying the effects of prepulse stimuli are likely to be different.

## Prepulse effects on the blink reflex in humans

Prepulse modulation of the eyeblink component of the startle reaction in humans is typically measured on the EMG activity recorded from the OOc muscle, induced by either a startling stimulus or a trigeminal nerve stimulus (Graham, 1975; Ison *et al.*, 1990; Valls-Solé *et al.*, 1999). Electrical stimulation of the supraorbital nerve elicits two responses in the OOc muscle. The first (R1) is an early response confined to the ipsilateral side of the stimulus, mediated by an oligosynaptic pontine circuit, probably located in the vicinity of the main sensory nucleus of the trigeminal nerve (Kimura, 1975; Ongerboer de Visser, 1983). The second (R2) is a late bilateral response, mediated by a circuit descending with the spinal tract of the trigeminal nerve in the pons and medulla

oblongata before reaching the pontomedullary reticular formation (Ongerboer de Visser and Kuypers, 1978). From there, impulses are relayed by a medullary pathway that ascends bilaterally to reach the facial nuclei in the pons. Thus, the reflex pathways mediating the R1 and R2/R2c responses share common afferent and efferent nerve fibres and tracts, but differ in their circuits in the central nervous system. Therefore, modulatory changes that affect only one of the responses or the two responses in opposite directions, like those observed in our study, are probably due to interferences in the blink reflex arc at a central level (Ison *et al.*, 1990). The fact that significant changes in amplitude occurred at very short ISIs without concomitant change in latency can be taken as an argument in favour of the effects taking place at a central level, close to the site of the stimulus. If this was not the case, the effects of STN–DBS would have occurred at a certain delay. Central effects on the blink reflex circuit can occur in facial motoneurons, in interneurons of the trigemino-facial reflex circuit, in integrative centres for trigeminal nerve inputs or in parallel circuits modulating reflex excitability.

Prepulse effects have been previously examined on the blink reflex elicited by trigeminal nerve stimulation (Sanes and Ison, 1979; Boulu *et al.*, 1981; Hoffman *et al.*, 1981; Rimpel *et al.*, 1982; Ison *et al.*, 1990; Boelhouwer *et al.*, 1991; Rossi and Scarpini, 1992; Valls-Solé *et al.*, 1999). In all these studies, prepulse modulation of the R2 response of the blink reflex has paralleled the effects seen in the responses of the OOC to a startling stimulus, with only slight differences attributed to the conduction time of fibres of each specific sensory modality (Valls-Solé, 2003). Most prepulse stimuli induce biphasic modulation of the response-eliciting stimulus, with short latency facilitation followed by a relatively long-lasting inhibition (Graham, 1975; Hoffman *et al.*, 1981; Blumenthal and Gescheider, 1987; Ison *et al.*, 1990; Boelhouwer *et al.*, 1991; Reijmers and Peeters, 1994; Valls-Solé *et al.*, 1999). The inhibitory effects of prepulse stimuli are generally referred to in the literature as prepulse inhibition. Regarding facilitation, we should differentiate between two effects: shortening of response latency and increasing of response amplitude. Fewer studies assessed the effects on the latency of the responses (Graham and Murray, 1977; Hoffman and Ison, 1980; Stitt *et al.*, 1980; Ison *et al.*, 1990; Boelhouwer *et al.*, 1991; Valls-Solé *et al.*, 1999). In general, these studies report a latency facilitation at ISIs between 0 and 60 ms. Latency facilitation and size inhibition may coexist, which is consistent with the idea that the two phenomena are driven by different physiological mechanisms (Graham and Murray, 1977; Hoffman and Ison, 1980; Blumenthal and Gescheider, 1987; Reijmers and Peeters, 1994). The equilibrium between facilitatory and inhibitory effects might depend not only on the intensity of the prepulse but also on the timing of arrival and synchronization of the sensory input. Boelhouwer *et al.* (1991) suggested that some of the effects related to

paired stimulation might actually occur at a motoneuronal level.

The phylogenetic ubiquity of the prepulse inhibition phenomenon has led to speculation about its functional significance (Blumenthal, 1999). The first interpretation has been in terms of sensory gating, or perceptual filtering, the reduction of processing of, and distraction by, irrelevant or repetitive stimuli (Geyer and Braff 1987; Braff *et al.*, 1992). According to Graham's theory of protection of preattentive processing (Graham 1975, 1992), prepulse stimuli initiate two automatic processes, one increasing general arousal for identification of the lead stimulus and the other protecting the processing of the lead stimulus from interruption by any new stimulus.

### Circuits identified in prepulse inhibition

The circuit of prepulse inhibition has been delineated in experimental animals using acoustic stimuli as prepulses (Saitoh *et al.*, 1987; Swerdlow *et al.*, 1990; Koch *et al.*, 1992; Koch *et al.*, 1993; Swerdlow and Geyer, 1993; Inglis and Winn, 1995; Blumenthal, 1999; Swerdlow and Geyer, 1999; Swerdlow *et al.*, 2001). Since prepulse inhibition is observed in decerebrate animals by transection at the anterior end of the superior colliculus (Davis and Gendelman, 1977; Fox, 1979; Li and Frost, 2000), such an effect of acoustic prepulse stimuli must be mediated by brainstem structures located between the midbrain and the medulla. Among the most likely candidates for such a role are the subpallidal projections to the PPTg, and the cholinergic neurons of the PPTg that project to the nRPC (Semba *et al.*, 1990; Koch *et al.*, 1993; Li *et al.*, 1999) and to the thalamus (Swerdlow and Geyer, 1999). Li *et al.* (1998) and Li and Yeomans (2000) have shown that a brief stimulation of the PPTg elicits a prolonged inhibition of the startle reflex. There is evidence that this long-lasting inhibitory effect is mediated by metabotropic inhibition of nRPC neurons driven by muscarinic and GABA<sub>B</sub> receptors (Jones and Shannon, 2000a, b).

The brainstem prepulse circuit is modulated by inputs from the forebrain, such as the prefrontal cortex, thalamus, hippocampus and amygdala (Hitchcock and Davis, 1991; Koch, 1996; Swerdlow and Geyer, 1999; Swerdlow *et al.*, 2001), and from the basal ganglia, such as the nucleus accumbens, anteromedial striatum and the globus pallidus (Koch and Schnitzler, 1997; Swerdlow *et al.*, 2001). Human studies that assessed somatosensory and acoustic prepulse modulation of the startle response with functional and volumetric voxel-based morphometry MRI showed that the hippocampus, striatum and thalamus are activated and there is a positive association between prepulse inhibition and the grey matter volumes of these structures (Kumari *et al.*, 2003, 2005). The STN is not known to be part of the cortico-striato-pallido-pontine circuitry that regulates prepulse inhibition (Swerdlow *et al.*, 2001). Previous animal studies that used lesion and intracerebral infusion techniques have demonstrated that prepulse inhibition of acoustic startle is

regulated by GABAergic activity in the ventral pallidum, and that ventral pallidal efferents include major projections to the PPTg, STN and mediodorsal thalamus (Kodsi and Swerdlow 1995, 1997). In these studies, STN lesions failed to significantly modify the prepulse inhibition of the acoustic startle reflex, which is consistent with the interpretation that the effects of sSTNDBS should be explained by activation of bypassing circuits.

### Intracerebral circuits mediating prepulse effects induced by STN-DBS in humans

Similar to acoustic and somatosensory prepulses, sSTNDBS induced R1 facilitation and R2 inhibition. One striking difference between our observations and those reported with acoustic and somatosensory stimuli is that sSTNDBS induced these effects at very short ISIs (already present at 0 ms). This suggests that the mechanisms responsible for the prepulse effects of STNDBS have a short conduction time to the site where the effects are produced. The effects documented in our study do not necessarily have to be attributed to activation of STN efferents. There are many different circuits around the STN that could have been activated by the single electrical stimuli used in our study. It is known that intracerebral electrical stimulation activates structures near the cathode more likely than those near the anode, and fibre tracts that run parallel to the stimulation more easily than those that run perpendicularly (Nowak and Bullier, 1998; Ashby *et al.*, 1999). Also, the excitability of axons is much higher than cell bodies and large myelinated axons are much more excitable than unmyelinated axons (Ranck, 1975; Yeomans, 1990; Tehovnik, 1996; Nowak and Bullier, 1998). Therefore, predominant effects of sSTNDBS are probably due to activation of large axons as suggested by studies that measured the chronaxie of DBS-induced excitatory responses (Ashby *et al.*, 1998, 1999; Holsheimer *et al.*, 2000; Wu *et al.*, 2001). sSTNDBS could potentially generate orthodromic and antidromic action potentials in all fibre tracts in the vicinity. The observed effects could thus be due to activation of afferents to the STN, projections from the STN to other nuclei such as SNr, GPe, GPi and the cortex, or any other fibre tract connecting different structures. In our opinion, the best candidates to mediate the inhibitory effects reported here are the pallidofugal fibre tracts running parallel to the STN on their way to the PPTg (Parent and Parent, 2004), or the cholinergic fibres projecting from the PPTg to the thalamus, that have inhibitory actions on trigeminal afferents (Reese *et al.*, 1995; Strafella *et al.*, 1997; Ashby *et al.*, 1999).

Some clues from our results could help in determining a possible explanation for prepulse inhibition from sSTNDBS. Even though we have found similar prepulse effects on the R1 and R2 of the ipsilateral and contralateral side to sSTNDBS, the two main effects observed in our study (i.e. facilitation of R1 and inhibition of R2) may follow completely different circuits. In our view, sSTNDBS leaves a trace of

excitability in neurons of the many circuits activated directly or through the axons being depolarized. This should include the alpha-motoneurons of some cranial nerve and spinal cord nuclei if the stimulus is powerful enough to reach the corticonuclear and corticospinal tracts at the level of the internal capsule, as suggested by other authors (Ashby *et al.*, 1999; Khun *et al.*, 2004). Therefore, the mechanism to account for R1 facilitation could be the generation of a short latency excitatory post-synaptic potential in facial motoneurons that will be subsequently facilitating responses to inputs from the supraorbital nerve. Such mechanism would explain why we found similar effects in both sides to unilateral stimulation, because of the known bilateral projection of the corticonuclear tract.

If we assume that facilitation of R1 can be caused by an increase in motoneuronal excitability, then the explanation for the simultaneous inhibition of R2 should be searched for at a pre-motoneuronal level. The circuit of the R1 response is limited to the upper pons, whereas that of the R2 involves the pontomedullary reticular formation (Ongerboer de Visser and Kuypers, 1978). The fact that prepulse inhibition was limited to R2 while R1 did not show any inhibition suggests that the inhibitory effects of the sSTNDBS may be limited to responses integrated in the pontomedullary reticular formation. Prepulse inhibition takes place in both sides to a single unilateral stimulation, suggesting bilateral projections for the circuit of prepulse inhibition. This is known to occur with nuclei of the pontomedullary reticular formation. Therefore, the connections between the nRPC and the PPTg are well suited for the inhibitory effects observed with sSTNDBS, which is in accordance with the circuit of prepulse inhibition proposed in the literature on animal experimentation (Saitoh *et al.*, 1987; Swerdlow *et al.*, 1990, 2001; Koch *et al.*, 1992, 1993; Swerdlow and Geyer, 1993, 1999; Inglis and Winn, 1995; Blumenthal, 1999).

### Differences in prepulse inhibition between acoustic or somatosensory stimuli and sSTNDBS

According to current theories (Garcia-Rill, 1991; Inglis and Winn, 1995; Kretschmer and Koch, 1998), the basal ganglia are likely to exert their control over the prepulse circuits through the PPTg, which regulates the excitability of startle-related structures of the reticular formation. In Parkinson's disease patients, the PPTg would receive an increased excitatory input from the STN, together with an increased inhibitory input from the GPi and SNr (Inglis and Winn, 1995; Kretschmer and Koch, 1998). The net effect of these opposed inputs on cholinergic neurons of the PPTg may be inhibition because the GPi additionally receives reduced inhibitory influences via the direct (D1) striatal projection. This lack of D1 inhibition could contribute to an increased excitability of the GPi, and give rise to a relatively more powerful inhibitory action of the GPi on the PPTg in comparison with the



excitatory effect of the STN. A dysfunction of the PPTg has been reported in Parkinson's disease patients (Hirsch *et al.*, 1987; Jellinger, 1988; Zweig *et al.*, 1989), and this may be the reason why Parkinson's disease patients have a reduced prepulse inhibition of the blink reflex to acoustic and somatosensory stimuli (Valls-Solé *et al.*, 2004).

In agreement with previous studies, our patients had a reduced prepulse inhibition of the blink reflex to both somatosensory and acoustic prepulse stimuli. In the same patients, sSTNDBS caused an effective and significant inhibition of the blink reflex (>90%). We can only hypothesize what would be the mechanisms accounting for such difference. One possibility is that the dysfunction responsible for the loss of prepulse inhibition by acoustic and somatosensory inputs lies in circuits rostral to the PPTg that receive the input from the acoustic and somatosensory stimuli (i.e. the nuclei of the reticular formation such as the nRPC and its reciprocal connections to the PPTg). Another possibility is that sSTNDBS induces its effects at a point beyond the PPTg in the prepulse circuit. In favour of the first hypothesis is the fact that Parkinson's disease patients have an abnormal startle reaction (Vidailhet *et al.*, 1992), which points to a dysfunction in nuclei of the reticular formation. In favour of the second hypothesis is the fact that sSTNDBS is known to cause inhibitory effects by way of activating afferents to the thalamic nuclei (Strafella *et al.*, 1997; Ashby *et al.*, 1999). Further work is needed to test which one of the two hypotheses is correct.

Prepulse inhibition is a very ubiquitous phenomenon that has been used surprisingly less in neurophysiological studies of the central nervous system. The use of the STN–DBS electrodes for testing intracerebral circuits brings the possibility of testing many unsettled neurophysiological issues, an opportunity that should not be missed by those with interest in how the human central nervous system is organized.

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