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Inhibitory attentional control in patients with frontal lobe damage

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Abstract

The performance of a group of frontal lobe lesion and a group of frontal lobe dementia patients was compared with the performance of their respective matched normal control groups on two tests of inhibitory attentional control—the stop-signal reaction time task and a negative priming task. Both patient groups responded significantly slower than their respective normal control groups, but they showed only marginally significant selective impairments on the measures of inhibition. The data suggest that the specific inhibitory processes evaluated by these two tests are, in general, spared in patients with focal frontal lobe lesions or frontal lobe degeneration.

Keywords

Prefrontal cortex; Inhibition; Negative priming; Stop-signal; Attention

1. Introduction

It is widely accepted that frontal lobe damage causes impairments in inhibition. However, the term inhibition (and frontal disinhibition, respectively) is often used to describe two different aspects of this cognitive function. The first one is manifested in the realm of social conduct as social disinhibition, profanity, impulsivity, tactlessness, loss of social responsibility, and lack of respect for social conventions. The most famous case to illustrate these effects of prefrontal lobe lesions on social behavior is that of the landmark patient Phineas Gage (Harlow, 1848, 1868). Modern imaging techniques, which were used to reconstitute the accident and to determine the location of Gage's lesion, as well as the observations of other patients with similar anatomical and behavioral patterns, led to the hypothesis that social conduct regulation depends on the orbitofrontal cortex, or more specifically, on the ventromedial prefrontal cortex (Damasio, Tranel, & Damasio, 1990; Dimitrov, Phipps, Zahn, & Grafman, 1999; Eslinger, 1998; Saver & Damasio, 1991).

The other type of inhibition is a component of the process of selective attention and is manifested in the suppression of goal irrelevant stimuli. There are numerous lesion and neuroimaging studies suggesting the critical involvement of the frontal lobes in this type of inhibitory control but their findings are different and sometimes inconsistent with respect to the frontal regions found to subserve the particular attentional and inhibitory processes. Glosser and Goodglass (1990), Wilkins, Shallice, and McCarthy (1987), Woods and Knight (1986),

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and Rueckert and Grafman (1996) reported impairments in sustained attention in patients with right frontal lobe lesions (FLL). Stuss, Benson, Kaplan, Weir, and Della (1981) found that FLL patients were not impaired compared to matched normal control (NC) subjects on several attentional measures including the Stroop. Vendrell (1995) reported that the right pre-frontal lateral region appeared to be the most important region for maintaining correct Stroop performance, that left lobectomies did not impair Stroop performance, and that lesions in the anterior cingulate cortex (ACC) did not produce selective changes in the Stroop effect, but simply resulted in increased reaction times in the non-interference condition. Two neuroimaging studies with normal subjects (Bench et al., 1993; Pardo, Pardo, Janer, & Raichle, 1990) concluded that the right ACC plays a role in the attentional aspects of the Stroop task. Deficits in selective attention in patients with right frontal lobe lesions were observed in several studies (Alivisatos & Milner, 1989; Knight, Hillyard, Woods, & Neville, 1980, 1981), whereas Lee, Wild, Hollnagel, and Grafman (1999) reported that the cognitive processes underlying visual selective attention and response competition as measured by a task based on space and target feature identity were, in general, spared in patients with frontal lobe lesions. In a neuroimaging study by Corbetta, Miezin, Dobmeyer, Shulman, and Petersen (1991), it was found that selective attention during visual discrimination of shape, color, and speed tasks induced activation in the basal ganglia, the lateral orbitofrontal (OF) cortex, and the premotor cortex. Effects of right and left OF lesions on different interference measures were reported in several studies (Fuster, 1985; Posner, Early, Reiman, Pardo, & Dhawan, 1988; Stuss et al., 1982), while Milner, Petrides, and Smith (1985) reported an effect of dorsolateral prefrontal lesions on interference. The lack of specificity and the inconsistency in some of these results might be due to the different etiologies, different lesion localization, and different ways in which the attentional and inhibitory processes were tested and measured (Stuss et al., 1999).

Stuss et al. (1999) suggested that clearly distinguishing among possible anterior inhibitory attentional processes would facilitate research in attention. In the present study we also adopted the approach of fractionation of the inhibitory mechanisms of selective attention in order to evaluate several specific aspects of inhibitory control in patients with frontal pathology and to try and identify the precise anatomic correlates of any observed cognitive impairments. We studied a homogenous group of patients with well-documented focal frontal lesions and a group of patients with frontal lobe dementia (FLD)—a progressive bilateral fronto-temporal cortical degenerative disease in which cognitive deficits, including distractibility, impulsivity, and disinhibition, often accompany personality and behavioral changes (Elfgren, Ryding, & Passant, 1996; Filley, Kleinschmidt-De Masters, & Gross, 1994; Frisoni et al., 1995; Gregory & Hodges, 1996; Miller, 1997; Moss, Albert, & Kemper, 1992; Talbot, 1996) that are similar to, but generally more severe than the ones observed in patients with focal frontal lobe lesions (Damasio, 1996; Grafman, 1989; Hecaen & Albert, 1978). We employed two tasks: a stop-signal reaction time task, developed by Logan and colleagues (Logan, Cowan, & Davis, 1984; Schachar, Tannock, Marriott, & Logan, 1995; Williams, Ponesse, Schachar, Logan, & Tannock, 1999), and a lexical negative priming task, extensively used by Hasher and colleagues (Kane, Hasher, Stoltzfus, Zacks, & Connelly, 1994).

The inhibitory control functions of human and non-human primates with frontal damage have been evaluated predominantly using the go/no-go task. Damage to the DLPFC has been found to impair response inhibition in monkeys in the studies of Iversen and Mishkin (1970), Butters, Butter, Rosen, and Stein (1973), and Sasaki, Gemba, and Tsujimoto (1989). A number of other studies reported that patients with frontal pathology were impaired on the go/no-go task (Decary & Richer, 1995; Leimkuhler & Mesulam, 1985). The involvement of frontal areas in response inhibition has been also documented in several neuroimaging studies, which employed the go/no-go task in humans. DLPFC activation during mixed go/no-go trials minus go trials was observed in a PET study by Kawashima et al. (1996) and in a blocked fMRI study by Casey et al. (1997). The right inferior prefrontal cortex was found to be involved in inhibition

during no-go trials in an event-related fMRI study by Konishi et al. (1999). Right DLPFC dominance for inhibitory function was observed in an event-related fMRI study by Garavan, Ross, and Stein (1999), in which a paradigm similar to the go/no-go one was utilized.

The stop-signal task we employed is a computerized measure of inhibitory control similar to the go/no-go tasks, but designed to isolate the inhibitory processes more effectively. The stop-signal type of inhibition is conceptualized as one of several internally generated acts of control in the repertoire of a higher order executive system that regulates behavioral execution (Goldman-Rakic, 1987; Shallice, 1982). The stop-signal procedure is a laboratory analogue of a situation that requires an individual to stop a planned or prepotent response. On the stop-signal task, a subset of trials from a series of regular choice reaction time trials is interrupted by a stop signal (Logan et al., 1984), which instructs the subjects to withhold the response that was in preparation. It becomes harder to suppress a response as the stop signal is presented closer to the go-signal induced moment of responding. A profile of inhibitory efficiency over time is derived by manipulating the stimulus onset asynchrony between the go-signal and stop signal. The stop-signal reaction time indicates the speed of the inhibition process.

Negative priming refers to the slowing of responses to targets which were distractors in immediately preceding trials (prime trials followed by probe trials) and could be viewed as an indication of inhibition, which is a normal component of selective attention. Metzler and Parkin (2000) reported reversed negative priming following frontal lobe lesions: whereas all control groups revealed robust negative priming, the majority of FLL patients showed positive instead of negative priming. Thus, a negative priming task appears to be a good instrument to detect inhibition deficits associated with frontal lobe damage. The negative priming task we employed in the present study was extensively used by Hasher and colleagues to evaluate the effects of age on inhibitory attentional mechanisms (Kane et al., 1994). Subjects are required to respond to target items presented simultaneously with a similar distractor item. On critical pairs of trials, the distractor item from the previous trial becomes the target item. On such “distractor suppression” trials, subjects' response times to the target are slowed compared to their responding when there is no relationship between distractors and targets. This slowed response, called suppression or negative priming, is believed to result from inhibition directed towards the previously selected-*against* distractor item, which is now a target.

The goal of the present study was to add to the understanding of the inhibitory mechanisms of selective attention and to identify their anatomical substrate. We expected to find both the FLL and the FLD patient groups impaired on these two inhibition tasks with poorer performance on the stop-signal task. We also attempted to indirectly compare the two patient groups in order to evaluate the effect of focal frontal lobe lesions vs. frontal cortical degeneration on inhibitory processes.

2. Experiment 1—Stop signal task

2.1. Subjects

2.1.1. FLL patients—Twenty-two patients (21 male and 1 female) with non-progressive frontal lobe lesions (7 unilateral left, 5 unilateral right, and 10 bilateral) participated in the study. Twenty of these patients were veterans who received penetrating missile or shrapnel wounds during the Vietnam War, and two patients had undergone surgery, one due to aneurysm and another to tumor. The two surgical patients were tested 1 and 7 years post-operatively. All lesions were confined to the frontal lobes with the exception of two patients whose bilateral lesions extended slightly into small border areas of the temporal lobes and one patient whose bilateral frontal lesion extended slightly into the parietal lobe. At the time of their evaluation, the patients' age ranged between 44 and 70 years (M = 53:8; SD = 7:3) and their education ranged between 10 and 18 years (M = 13:7; SD = 2:1).

All FLL patients were administered the SST and their performance on all measures was compared with the performance of 22 age (*M* = 52:5; *SD* = 7:8) and education (*M* = 14:3; *SD* = 1:8) matched normal controls. The demographic characteristics of the FLL patients and their matched controls as well as the patients' general cognitive performance and SST and NPT scores are given in Table 1.

The SST results of the FLL patients were compared with their results from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981), the Wechsler memory Scale (WMS) (Wechsler, 1974), the Wisconsin Card Sorting Test (WCST) (Berg, 1948), the Tower of Hanoi (TOH) (Glosser & Goodglass, 1990), and the Beck Depression Inventory (BDI) (Beck, 1996), in order to probe for possible interconnection between general cognitive and executive functioning and SST performance, as well as with their UCLA Neuropsychiatric Inventory (NPI) disinhibition score (Cummings et al., 1994). Precise individual charts of damaged frontal brain regions were drawn based on individual head CT or MRI scans available for 20 of the patients using the method of Damasio and Damasio (1988). Each individual lesion chart was represented as a vector of zeros and ones, indicating absence or presence of damage for all frontal Brodmann areas (Table 2). Estimated measures of left, right, and total brain volume loss in cm^3 were available for 19 of the patients. The FLL patients' SST performance was analyzed for effects of lesion side, site, and size.

2.1.2. FLD patients—Fifteen patients (10 male and 5 female), clinically diagnosed with FLD according to the Lund and Manchester research criteria (1994), aged between 45 and 76 years (*M* = 61:4; *SD* = 8:3) and educated between 12 and 20 years (*M* = 15:7; *SD* = 2:4), were included in the study. Their results on all SST measures were compared to those of 15 normal control subjects, who were matched for age (*M* = 62:0; *SD* = 9:1) and education (*M* = 16:0; *SD* = 2:3) with the FLD patients. In order to see whether negative priming depends on the general cognitive status and executive functions of the patients, the SST performance of the FLD group alone was compared with their performance on the TOH, WCST, Mattis Dementia Rating Scale (MDRS) (Mattis, 1988), and BDI. The demographic and basic cognitive data as well as the NPT and SST scores for the FLD patients and their matched NCs are given in Table 3.

All participating subjects understood the test instructions and gave their written informed consent to participate in the study, which was approved by the Institutional Review Board.

2.2. Procedure

The task consisted of two types of trials: primary task trials and stop-signal trials. On primary task trials, the letters X or O were presented in the center of the computer screen and the subjects responded by pressing the corresponding key on the keyboard. On stop-signal trials, the X and O were presented along with a tone, or stop signal, which instructed the subjects to inhibit their key press to the primary task stimulus. The tones were presented randomly across trials. The initial stimulus onset asynchrony (SOA) between the onset of the go signal and the onset of the stop signal was set to a value 250 ms faster than the subject's mean response time to the go-signal computed from the first block of trials. The subject sat in front of a monitor with their left and right index fingers on the two labeled X and O keys. For each trial, a fixation cross was presented at the center of the screen for 500 ms, followed by the letter for that trial for 1000 ms and then a blank screen for 1500 ms.

The subjects completed 12 blocks of trials for this task; each block consisted of 64 trials in two 32-trial sessions. The program stopped every 32 trials to give the subjects a break, so there were 24 stopping points. The first block served as a practice block. Its first 32 trials helped to familiarize the subjects with the task and yielded the mean reaction time used for determining the tone intervals for the second 32 trials. The subjects were instructed in the first part of the practice block (first 32 trials) to press the X or O key, respectively, as soon as they decided

which letter was presented but to ignore the tone they occasionally heard. After the first 32 practice trials, and for the rest of the experiment, the subjects were asked to still press the appropriate key as quickly as they could whenever they saw the X or O but to try to stop their response each time when they heard the tone. Subjects were told that the tone occurred at different times, relative to the onset of the X and O, so sometimes they would be able to stop and sometimes they would not. They were also asked not to wait to see if a tone sounded before responding and still try to respond as quickly as possible when the X and O appeared.

The program registered the go-signal response time and estimated the stop-signal response time using the method described in Williams et al. (1999). Stop signal delay (SOA) was manipulated by a tracking algorithm that was designed to find the SOA at which subjects inhibited 50% of the time. The tracking algorithm increased SOA by 50 ms whenever subjects successfully inhibited their response on a stop trial and it decreased SOA by 50 ms whenever subjects failed to inhibit their response on a stop trial. The stop-signal response time indicated the speed of the inhibition process and was the variable of primary interest. In addition, two other variables were recorded for each participant: the accuracy of go-task responding and the probability to inhibit the go-task response given a stop signal. Data from the first test block were excluded from all analyses because the tracking algorithm required a few trials to adjust to individual participants.

2.3. Results

2.3.1. NC group—All NC participants who were given the SST ($n = 37$) were divided into two subgroups—middle aged (40–59 years; $n = 23$) and old subjects (60–76 years; $n = 14$). There was no effect of gender or education. The older NC subgroup was significantly slower on the mean RT measure (F (1, 35) = 9.12; $p < .01$), but there was no significant difference between the two subgroups on the stop-signal RT measure.

2.3.2. FLL patients—The SST performance of the FLL patients was compared with the performance of their matched normal controls. ANOVA revealed that the FLL patients were significantly slower on the mean response time measure ($F(1, 42) = 7.18$; $p < :01$). There were no between-group differences for the stop-signal response time measure, which indicated the speed of inhibition process, the accuracy of go-task responding, or the probability to inhibit the go-task response given a stop signal. For the FLL group, there was no effect of lesion lateralization on any SST measures, but there was a marginally significant effect of ACC involvement ($F(1, 17) = 4.32$; $p = .053$) only on the mean response time measure, in which patients with ACC lesions were slower. There was a significant effect of total brain volume loss on overall accuracy ($F(1, 15) = 7:8$; $p < .05$). The stop-signal response time measure was not correlated significantly with the mean response time measure. It appeared that the stop-signal response time measure was highly significantly correlated with the NPI disinhibition measure ($r = .84$, $p < .01$), but this correlation became non-significant after excluding from the analysis a single FLL patient with an extremely high NPI disinhibition score. The stop-signal response time measure was moderately significantly correlated with the vector representing damage to left Brodmann area 6 ($r = .47$, $p < .05$), perhaps because of the planned motor response withholding component of the task. No significant correlations between SST performance and performance on other neuropsychological tests or the BDI total score were found.

2.3.3. FLD patients—The comparison of the SST performance of the FLD and NC groups by ANOVA revealed that the FLD patients were significantly slower ($F(1, 26) = 7.81$; $p < .01$), significantly less accurate ($F(1, 25) = 9.81$; $p < .01$), and marginally less able to inhibit their response ($F(1, 19) = 4.0$; $p = .061$). For the FLD group, there was a significant effect of frontal or temporal involvement on the SST mean response time measure ($F(1, 9) = 10.4$; $p < .$

01), on which patients with only frontal involvement were significantly slower than patients with fronto-temporal involvement. There were no significant effects of age, disease onset and duration, and general cognitive status on any SST measure, but there was a significant effect of gender on the mean response time measure ($F(1, 13) = 16.42$; $p < .01$), on which women were significantly slower. As in the FLL group, the stop-signal response time measure was not correlated significantly with the mean response time measure.

2.4. Discussion

Both the FLL and the FLD patient groups in our study were significantly slower than their respective matched NC groups on the mean go-signal reaction time measure. The FLL patients were as accurate as their matched NCs in executing the go-response and as able as their matched NCs to inhibit their responses. In the FLL group alone, there was no effect of lesion laterality, patients with ACC involvement were marginally slower than patients without ACC involvement, patients with large lesions were significantly less accurate in their responses, and slower response to the stop signal was associated with damage to left Brodmann area 6. The FLD patients were significantly less accurate in their go-responses and marginally less able to inhibit their responses, which was not related to their general cognitive status, age, and disease onset and duration. It appears that the inhibitory process measured by the stop-signal variable is relatively spared in patients with FLL lesions and marginally impaired in patients with FLD.

The SST, developed by Logan and colleagues to study inhibitory control, is similar, although experimentally more rigorous than the go/no-go tasks, because the stop signal is presented closer (at controlled intervals) to the go-signal induced moment of responding. The SST has been successfully used to study normal and patient populations. Williams et al. (1999) employed it to study development of inhibitory control across the life span and found that the ability to inhibit prepotent responses improved throughout childhood and then diminished slightly throughout adulthood. Deficient inhibitory control in attention deficit hyperactivity disorder was detected using the SST in several studies, e.g., Aman, Roberts, and Pennington (1998), Oosterlaan and Sergeant (1998), and Schachar et al. (1995). The SST was also used to evaluate pharmacological effects on inhibition in hyperactive children (Tannock, Schachar, & Logan, 1995) and in young women with traits of anxiety (Schuck et al., 1998). Mesial hypofrontality in adolescents was observed in an fMRI study, which utilized the SST (Rubia et al., 1999). In our study, which employed the SST to study patients with focal and degenerative frontal lobe damage, the SST was unable to detect significant inhibitory impairments in the two frontal patient groups, suggesting that a different mechanism may be responsible for the inhibitory deficits observed mostly in attention deficit hyperactivity disorder using this paradigm.

3. Experiment 2—negative priming task

3.1. Subjects

3.1.1. NC subjects—Sixty-four normal subjects (94% right-handed, 45 male and 19 female), between the ages of 13 and 76 ($M = 34.6$; $SD = 18.9$) with between 7 and 20 years of education ($M = 13.9$; $SD = 3.3$) were recruited for this study. None of the subjects reported any history of alcohol or drug abuse or neurologic or psychiatric illness. All subjects were administered the negative priming task (NPT) and their scores on the different measures of the test were analyzed for the effects of age, education, handedness, and gender.

3.1.2. FLL patients—Sixteen of the FLL patients described in Experiment 1 and their matched NCs were administered the NPT (Table 1). In addition, the NPT results of the patients were compared with their results from the tests of general cognitive abilities, executive

functions, and disinhibition listed in Experiment 1. The FLL patients' NPT performance was also analyzed for effects of lesion side, site, and size.

3.1.3. FLD patients—Nine of the 15 FLD patients who participated in Experiment 1 and their matched controls were administered the NPT (Table 3). The NPT performance of the FLD group alone was compared with their performance on the TOH, WCST, MDRS, and BDI.

3.2. Procedure

Subjects were seated in front of a standard personal computer screen at a comfortable distance in a dimly lit room. A voice-activated relay was used to record the onset latency of the subjects' verbal responses to the targets. Subjects briefly practiced with the microphone by reading numbers presented on the screen. There was one demonstration trial, during which subjects were given the instructions, followed by 10 practice trials. Subjects were told that they would be presented with series of word pairs in which one of the words would be red and the other one green, and they would have to respond to the green word and ignore the red word. At the beginning of each trial, a ready signal (“READY?”) appeared on the screen. To begin the trial, the subjects had to press the space bar. The time between trials was thus controlled by the subject, allowing him/her to take a break if desired. After a 1500-ms delay from the depression of the keyboard, a fixation cross appeared for 250 ms at the center of the screen. Next, a word pair was presented for 300 ms. One word appeared slightly above the fixation cross, one slightly below; the target appeared in either location with equal frequency. Subjects were instructed to respond as quickly and as accurately as possible to the green word. Each trial consisted of two such presentations. The first pair was referred to as the prime display, and the second as the test display. Subjects responded to both displays but only the response to the test display was of interest. In the no-distractor condition described below, only a single green word appeared. Each letter of each word was immediately masked for 100 ms by a symbol composed of overlapping red and green lines. A blank screen was then shown for 1500 ms, after which the sequence of the fixation cross, word pair, and masking symbols were repeated for an identical duration. This resulted in a 1850-ms interval between the offset of the prime pair and the onset of the target pair. After each trial, the subject's response times were displayed for 300 ms. No feedback was given on word accuracy. There were nine different stimulus words used, all of which were presented in capital letters: BAG, POT, GIN, ROD, CAT, JAR, TIE, CUP, and FUN. These words were all nouns with frequencies between 10 and 50 per 1,000,000 words, three letters in length, non-rhyming, non-synonymous, and not having associative meaning when presented together.

There were five trial types in the experiment: control, distractor suppression, repeated distractor, target to distractor, and no distractor. In the control trials, the target in the test word pair had no relation with the target or distractor in the prime word pair. In the distractor suppression trials, the distractor in the prime pair became a target in the test pair. In the repeated distractor trials, the same distractor word was used in both the prime and test pair. In the target to distractor trials, the target in the prime pair became distractor in the test pair. In the no distractor trials, the prime pair had a distractor, but the test pair contained only the target word.

One hundred and eighty experimental trials were administered to each subject, 36 of each trial type. The order of trial types was pseudo-random, and no condition occurred three times in a row. Every possible word pair combination appeared twice in each trial type, with each word being used once as the target item of the pair and once as the distractor, and with each of these combinations being used once as a prime display and once as a test display. Each stimulus word appeared four times in each possible function (prime target, prime distractor, test target, and test distractor) in each trial type, with the exception of the no distractor trial type, in which there were only three functions (prime target, prime distractor, and test target).

The computer recorded the reaction times to the five trial types, which were measured from the onset of the stimulus array to the onset of the subject's response. Errors in voice naming and voice key failures were recorded by the experimenter. Each time the subject responded in less than 300 ms or there were other microphone related errors, the computer recorded reaction times of 0 ms, which were subsequently deleted from the data file by the experimenter. In addition to the five reaction time measures and the error type measures, four contrast measures were computed. The difference between the reaction time on the distractor suppression condition, where the distractor from the previous trial becomes a target, and the control condition, where the target in the test word pair had no relation with the target or distractor in the prime word pair, yielded the negative priming measure. The difference between the reaction times for the control condition and the reaction times to repeated distractor and target-to-distractor conditions yielded two measures of a facilitation effect. The difference between the reaction times for the control condition and the no distractor condition, i.e., response time slowing in the presence vs. absence of a distractor, represented the interference measure. The negative priming measure was of primary interest for the analysis since it reflected quantitatively the process of inhibition.

3.3. Results

3.3.1. NC group—The performance of all of the normal subjects on all NPT measures was first analyzed for effects of age, gender, and condition. The whole control group was divided into four subgroups with respect to age: adolescents (n = 13; 13–16 years), young adults (n = 23; 17–25 years), middle-aged adults (n = 19; 39–59 years), and older adults (n = 9; 60–76 years). The reaction times profiles across the five conditions were parallel for all four age groups, with the young adults being the fastest, followed by the adolescents, the middle aged adults, and the older adults being the slowest. The repeated measures ANOVA of the five reaction time variables produced a significant effect of age ($F(3, 58) = 3.25$; $p < .05$) and trial type ($F(4, 232) = 186.0$; $p < .0001$) but the interaction was not significant. There were no significant effects for age, gender, or handedness on the negative priming, facilitation and interference measures. There was a significant age effect for total error rate ($F(3, 53) = 4.11$; $p < .05$), on which the adolescents made the most errors and the middle-aged adults made the least errors. Gender or handedness effects on the error rate measure were not found. Planned comparisons of the reaction times for the five trial types within each age group showed that all age groups, except the older adults, demonstrated a negative priming effect, i.e., the difference between the reaction time on the control trials and distractor suppression trials was significant in all age groups but the older adult group. This result generally replicated the results of Kane et al. (1994).

3.3.2. FLL patients vs. NCs—There was no significant effect of group on the error rate and five reaction time measures. The reaction time profiles of the two groups ran in parallel with the FLL group marginally slower on all five conditions. Although there was no significant group effect on the negative priming contrast measure, when planned comparisons of the five reaction time measures were run separately for the NC and FLL group, they revealed that the difference between the reaction times in the control condition and the distractor suppression condition were significant for the NC group ($p < .01$) but not for the FLL group ($p = .16$). This indirect comparison indicated that the FLL patients' negative priming was modestly impaired. The negative priming contrast variable was not correlated significantly with any of the verbal perseveration measures—FAS, supermarket, animals, or countries.

There was no significant effect of side of frontal lesion on any NPT measure. There was a significant interaction effect of side of lesion by condition ($F(8, 52) = 2.2$; $p < .05$). Left FLL patients were faster than the patients with right and bilateral lesions on all reaction time measures, but their profile was flat with no negative priming or facilitation peaks. There was

no significant interaction between lesion side and type of contrast by ANOVA. The Pearson product–moment correlations between total brain tissue volume loss and the NPT measures were not significant. When patients with small (less than 41.7 cm^3) and large (more than 41.7 cm^3) lesions were compared, the effect of group was not significant. Next, the FLL patient group was divided into two subgroups, depending on whether they had documented evidence of anterior cingulate gyrus involvement, but there were no significant group differences by ANOVA. The comparison of FLL patients with predominantly dorsolateral and predominantly orbitofrontal lesions did not yield significant differences, either. The negative priming measure was significantly correlated with the vectors representing damage to right Brodmann areas 9 ($r = .71$, $p < .05$) and 32 ($r = .78$, $p < .05$).

Pearson product–moment correlations were computed between the general cognitive and executive functioning scores (only available for the FLL patients) and NPT measures in order to find possible dependence between general cognitive status and negative priming. There were no significant correlations between the negative priming measure and any general cognitive variable or the NPI social disinhibition measure.

3.3.3. FLD patients vs. NCs—The FLD patients were significantly slower ($ps < .01$) than their matched NCs on all five NPT conditions. The higher total error rate of the FLD group compared to the NC group almost reached significance ($p = .072$). There was no group effect on the negative priming measure and there was no interaction between group and trial type. However, planned comparisons performed separately for the FLD patients and for the NC group showed that the difference between the control condition and the distractor suppression condition, representing the negative priming effect, was statistically significant in the NC group ($p < .01$) but it was not significant in the FLD group, indicating an impairment in inhibition. This NC group, composed of subjects from the whole NC group matching the FLD patients for age, gender, and education, was younger (mean age = 61.4, $SD = 8.3$) than the older control subgroup used in the analysis of demographic effects (mean age = 67.6, $SD = 6.8$). The lack of significant negative priming effect observed in the older control group on one hand, and the significant negative priming effect observed in the NC group matching the FLD patients, on the other hand, may be due to the age difference between the two older groups.

Significant effects of disease onset or duration were not observed. The total NPT error measure was significantly correlated with dementia severity assessed with the MDRS. The NPT negative priming variable was not correlated significantly with any standard neuropsychological test measure or the total BDI coefficient, excluding depression as a factor. Similar to the FLL group, it appeared that although NPT accuracy and general cognitive test performance were interrelated, negative priming as measured by the NPT was not.

Next, the FLD group was divided into two subgroups: patients with only frontal and patients with fronto-temporal damage, according to the CT or MRI scans available for most of the patients. Analysis of variance by lesion site was not significant for the total error rate, reaction time and contrast NPT measures, but it was borderline significant ($p = .067$), with the subgroup with fronto-temporal lesions showing a smaller negative priming effect, i.e., impaired inhibition. This trend should be interpreted with caution considering the small number of patients in each subgroup.

3.4. Discussion

Lexical negative priming in our experiment was defined as a slowing of response times on distractor suppression trials as compared to control trials, in which there was no relationship between the words of the prime and test pairs.

The analysis of the NPT performance of the four NC groups revealed the following results: the older the subject, the slower they responded; adolescents made the most errors; and the oldest adults showed no negative priming. This last result is in concordance with the results of Kane et al. (1994), who developed and used the NPT to compare two groups of normal subjects —younger and older adults, and showed that negative priming is absent in elderly subjects. With the goal of determining how negative priming varies with age, at what age the anatomical substrate responsible for negative priming matures, and at what age it begins to decline, we compared the performance of four age groups: adolescents, young adults, middle aged adults, and older adults. It appeared that by the age of 14 the mechanisms for negative priming have fully matured.

According to the hypothesis that negative priming is based on prefrontal cortex mechanisms, we expected to find significant effects of frontal lobe lesions on NPT performance and to be able to identify the precise anatomical structures subserving negative priming. We observed general cognitive slowing as a result of having a frontal lobe lesion—the FLL patients were marginally slower than their matched NC subjects on all reaction time measures. The total brain tissue loss volume was not related with the NPT performance, neither was the involvement of the ACC. The negative priming of the whole FLL group appeared impaired—there was no significant difference between the reaction times on the control and distractor suppression condition. There was no significant effect of side of frontal lesion on any NPT measure but there was a significant interaction effect between side of lesion and trial type, where left FLL patients did not show slowing in the distractor suppression condition as a result of negative priming, which might have contributed to the observed lack of negative priming in the whole FLL group. The observed effect of left FLL on the negative priming process might be due to the lexical character of the task. Since it was not possible to subdivide the FLL group into two subgroups with strictly dorsolateral or strictly orbitofrontal lesions, the FLL group was subdivided into two subgroups with predominantly dorsolateral and predominantly orbitofrontal lesions, and this very rough grouping might be the reason why the two subgroups did not differ significantly on any NPT measure.

Similarly to the FLL group, the FLD patients demonstrated general slowing on all NPT conditions, made more errors, and did not show significant slowing in the distractor suppression condition as a result of negative priming. As in the FLL group, the error rate of the FLD group was related with their general cognitive status. In both patient groups, the negative priming measure was not correlated with their scores on the general cognitive measures or BDI, which indicates that the impaired performance of both groups on the inhibition measure was not a result of their general cognitive decline or depression, neither could it be attributed to the age at which the disease onset occurred or the duration of the disease. There was a subtle effect of temporal lobe involvement in the FLD group—the negative priming effect shown by the FLD subgroup with both frontal and temporal involvement was marginally smaller than the one of the FLD subgroup with only frontal involvement.

A location-based negative priming task was used as a measure of selective attention in patients with focal brain pathology in a study by Stuss and co-authors (Stuss et al., 1999). They employed a spatial selective attention paradigm to evaluate patients with well-documented frontal lesions on three measures of selective attention: interference, negative priming, and inhibition of return. These investigators found that interference, negative priming, and inhibition of return were mediated by different brain regions and that their expression was modulated by the complexity of the selection task. Right frontal lobe damage resulted in a virtual loss of negative priming, and left and bilateral frontal damage resulted in diminished negative priming.

It appears that there is an inconsistency between our results and the results of Stuss et al. (1999). The most impaired group on their negative priming subtest was the right frontal group, whereas in our study it was the left frontal group. There are two factors that might have contributed to this discrepancy. The first one includes the different etiologies of the FLL patient groups in the two studies. The FLL patients in the Stuss et al. study had typically suffered a stroke or a tumor. All but two of our FLL patients had received penetrating wounds several decades prior to the study. The second factor includes the different techniques by which the negative priming phenomenon was evaluated and the different modalities (lexical vs. spatial) in which the stimuli were presented, which might have led to the different lesion groups (left vs. right) found to be impaired on the two tasks. It might be helpful to utilize both techniques in the same FLL group in order to precisely describe the effect of lesion lateralization on performance. Connelly and Hasher (1993) showed no lexical negative priming for older adults, but reliable spatial negative priming, which suggests some independence of the two processes.

4. General discussion

We found that negative priming as measured by the NPT was moderately impaired in FLL and FLD patients in comparison with their respective matched controls (and that it was associated with right Brod-mann areas 9 and 32). We also found that stop-signal inhibition measured with the SST was generally spared in FLL patients and marginally impaired in FLD patients in comparison with their respective NC groups (and that it was associated with Brodmann area 6 on the left). This lack of robust differences between the patients with focal frontal lesions or frontal degeneration and their controls on the two tasks of inhibitory control we utilized could be due to several reasons.

First, negative priming and stop-signal inhibition may be spared in these two patient groups. It is difficult to accept this conclusion, which is in contrast with most studies, which employed similar techniques and found that frontal damage resulted in impaired inhibitory control. However, there are a few studies with findings similar to ours. Stuss et al. (1981) reported negative results on the Stroop and other measures of attention in a group of frontal lobectomy patients. In the same FLL population that we studied, Lee et al. (1999) found no significant impairment on the flanker selective attention task. Second, the main variables of interest in both tasks were results of subtraction of RT measures, which might have canceled out significant group differences. In order to exclude such a possibility, we repeated all analyses using log-transformed and normalized variables and the results were identical to the results obtained using the raw data. Third, it is possible that our FLL patients, who formed a homogenous group with old, stabilized lesions, are qualitatively different from all FLL samples tested in the other studies. In fact, in the only two studies reporting results similar to ours, the FLL patient groups were also very similar in etiology. In the report of Stuss et al. (1981), where the FLL group was found to be not impaired on the measures of inhibitory control, all patients underwent lobectomy about 20 years prior to the study. Most of our FLL patients suffered frontal injuries also about 20 years prior to the study. Like out FLL patients in the present study, the FLL patient group in the study of Lee et al. consisted of Vietnam veterans. However, this could not explain the negative results in the FLD group.

It is also possible that (as suggested by Stuss et al. (1981) as an explanation of their negative results) in the testing situation, which is structured, with rigid demand for compliance, the examiner acts as the “frontal lobes” for the patients. Next, the negative priming effects even in the normal population are small and require large samples. We may have gotten more robust effect, if each patient were matched with not one, but a group of NCs, as in the study of Metzler and Parkin (2000). Likewise, the SST, and especially the tracking algorithm, which has been consistently found to be sensitive in assessing inhibitory deficits in ADHD, might neither be sensitive nor specific enough to detect impairment in FLL because of the different types of

frontal pathology involved in adults with head injuries or frontal degeneration and hyperactive children.

Interestingly, the standard deviations in the FLL and FLD patient groups were much larger than those of the matched NC groups on most NPT and SST measures. May and Hasher (1998) reported that inhibition was better for normal subjects when they were tested closer to their optimal than their non-optimal time. It is possible that changes in inhibition may be mediated by circadian variations in frontal functioning and these variations may be more significant in patients with frontal pathology than in normal subjects.

Also, Stuss and Alexander (2000) have recently pointed out that patients with frontal damage are variable in their performance in that they could successfully do a task one day, but not another. The authors hypothesized that the ability to complete the task in these patients is intact, but they are unable to sustain the top-down effort to complete the task consistently, and that such variability very likely might confound experimental studies of frontal lobe functions.

The ACC is thought to play a role in inhibitory attentional control and conflict monitoring (Awh & Gehring, 1999; Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Carter et al., 1998, Carter, Botvinick, & Cohen, 1999; Gehring & Knight, 2000). Our results did not implicate the ACC in these processes. Kiehl, Liddle, and Hopfinger's (2000) analyses of inappropriate responses during a go/no-go task revealed extensive activation in the rostral ACC and in the left lateral frontal cortex, which they suggested was selectively activated for error processing (we also observed a tendency of left FLL involvement, unlike most other studies, in which the right frontal lobe was implicated). Gehring and Knight (2000) found in an ERP study that the lateral PFC seemed to interact with the ACC in monitoring behavior and in guiding compensatory systems. It is possible that we failed to confirm the above observations because breaking the FLL group into subgroups with lesions to different frontal areas resulted in a lack of power to detect between-group difference.

An interesting question, which we were not able to explore in the present study, is whether the same mechanisms are responsible for social inhibition and for lower levels of inhibitory control as the ones we attempted to assess. In the controlled vs. automatic attentional processes framework, social inhibition could be placed at the very controlled end of the continuum; stuck-in-set behavior and perseveration—typical FLL manifestations—in the middle; and negative priming, followed by inhibition of simple movement as in the SST—at the least controlled, almost automatic end of the continuum. This could justify the negative results in our FLD group—FLD patients are known for their social disinhibition, but lower levels of inhibition could be preserved.

It is widely accepted that attention is a system of cognitive control with different components having distinct anatomical and physiological bases, and that the highest levels of attentional control are based in the frontal lobes and are used to inhibit irrelevant stimuli in order to facilitate the most complex behaviors (Shimamura, 1995). Alexander, DeLong, and Strick (1986) described functional loops, linking the prefrontal cortex, basal ganglia structures, and motor cortex via the thalamus. The role of basal ganglia in inhibitory control of motor programs was suggested by several researchers (e.g., Kropotov & Etlinger, 1999; Mink, 1996). It is possible that impairment of different components of the network results in different inhibitory deficits. Recent neuroimaging studies attempted to finely dissociate the components of these integrated attentional networks (Casey et al., 2000; Liotti, Woldorff, Perez, & Mayberg, 2000). Liotti et al. (2000) conducted an ERP study of the temporal course of the Stroop interference effect and suggested that the Stroop color-word interference trial first activates the anterior cingulate cortex and then the temporo-parietal cortex. Casey et al. (2000), in an fMRI study using the flanker task found that modulating attentional conflict and stimulus

selection are separate aspects of attention. They observed a dissociation between the DLPFC and ACC, involved in conflict detection and control processes, and the visuospatial attentional system (superior frontal gyrus and superior parietal cortex), involved in selective attention. The authors were also able to distinguish between neural systems involved in different forms of conflict. Conflict that was associated with overriding highly salient events, e.g., incompatible trials after compatible trials, activated the ACC and DLPFC, whereas conflict that was caused by simple violations of expectation activated the basal ganglia and insula cortex.

The observed modest disruption of the inhibitory processes evaluated by the SST and NPT in the present study suggests that another component system of the very complex network may be most responsible for these processes. One candidate system could be the basal ganglia, which are extensively connected with both the ACC and PFC, and which have been found activated by expectancy violations by Casey et al. (2000).

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Table 1

Demographic data, basic cognitive, NPT and SST scores, and ANOVA *p* values for the FLL and NC groups (mean (*SD*))

	FLL	NC	ANOVA *p* values
N	22	22	
Age	53.8 (7.3)	52.5 (7.8)	.57
Education	13.7 (2.1)	13.7 (1.8)	.31
NPT			
Error rate	0.12 (0.09)	0.10 (0.09)	.44
Reaction times			
Control	619.1 (89.8)	582.8 (71.5)	.24
Distractor suppression	630.0 (98.5)	602.6 (76.6)	.41
Repeated distractor	616.9 (91.3)	583.2 (78.0)	.29
Target to distractor	608.0 (88.5)	578.9 (83.8)	.36
No distractor	552.3 (65.1)	523.3 (77.7)	.28
Contrasts			
DS–C	10.9 (24.7)	19.8 (20.9)	.30
C–RD	2.3 (17.0)	−0.4 (15.6)	.66
C–TD	11.0 (21.9)	3.9 (21.4)	.38
C–ND	66.8 (35.2)	59.5 (22.2)	.51
SST			
Mean RT	666.5 (119.7)	573.2 (111.1)	.010*
Accuracy	96.8 (3.0)	96.0 (8.9)	.72
Probability to stop	0.51 (0.11)	0.52 (0.04)	.99
Stop signal RT	282.1 (145.9)	242.42 (75.1)	.26
WAIS-R			
Verbal IQ	96.9 (12.9)		
Performance IQ	100.5 (12.1)		
Full IQ	98.6 (13.8)		
TOH	1008.6 (314.7)		
WCST			
Categories	4.6 (2.1)		
% perseveration	18.6 (18.4)		
BDI	9.6 (7.2)		
NPI	8.6 (8.6)		
Total brain volume loss [sm^3]	65.3 (48.8)		

DS, distractor suppression; C, control; RD, repeated distractor; TD, target to distractor; ND, no distractor; and RT, response time. *p* values significant at the 0.05 level are marked with *.

Table 2

Individual lesion sites and lateralization

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Lesion side	R	L	B	B	B	B	L	L	B	R	B	L	R	L	B	R	B	L	L	B	R	B
BA4L	0	1	0	0	na	0	0	na	1	0	0	0	0	0	0	0	0	0	0	0	na	0
BA4R	0	0	0	0	na	0	0	na	1	1	0	0	0	0	0	0	0	0	0	0	na	0
BA 44L	0	1	1	1	na	0	0	na	1	0	0	0	0	0	0	0	0	0	1	1	na	1
BA44R	0	0	1	0	na	0	0	na	1	0	0	0	0	0	0	1	0	0	0	0	na	0
BA45L	0	1	0	0	na	1	0	na	0	0	0	1	0	1	0	0	0	1	1	1	na	1
BA45R	0	0	0	1	na	0	0	na	0	0	1	0	1	0	1	1	0	0	0	1	na	0
BA47L	0	0	0	0	na	0	0	na	0	0	0	0	0	0	0	0	0	0	0	0	na	0
BA47R	0	0	0	0	na	0	0	na	0	0	0	0	0	0	0	0	0	0	0	0	na	0
BA6L	0	1	1	0	na	0	0	na	1	0	0	0	0	0	0	0	1	0	1	1	na	0
BA6R	0	0	1	0	na	0	0	na	1	0	0	0	0	0	1	0	0	0	0	0	na	0
BA10L	0	1	1	1	na	1	1	na	0	0	1	0	0	1	0	0	1	0	1	1	na	1
BA10R	0	0	1	1	na	1	0	na	0	1	1	0	0	0	0	0	1	0	0	1	na	0
BA9L	1	1	0	0	na	0	0	na	1	0	1	0	0	0	0	0	1	0	1	0	na	0
BA9R	0	0	0	0	na	0	0	na	0	1	1	0	1	0	0	0	1	0	0	0	na	0
BA8L	0	1	0	0	na	0	0	na	1	0	1	0	0	0	0	0	1	0	0	0	na	0
BA8R	0	0	0	0	na	0	0	na	1	0	1	0	0	0	0	0	1	0	0	0	na	0
BA46L	0	1	1	0	na	1	1	na	1	0	1	1	0	1	1	0	1	1	1	1	na	1
BA46R	0	0	1	1	na	1	0	na	0	1	1	0	1	0	0	1	1	0	0	1	na	0
BA32L	0	1	0	1	na	0	1	na	1	0	1	0	0	1	1	0	1	0	1	0	na	1
BA32R	1	0	0	1	na	0	0	na	1	1	1	0	1	0	1	0	1	0	0	0	na	0
BA11,12L	0	1	1	1	na	1	1	na	0	0	1	0	0	1	0	0	0	0	1	1	na	1
BA11,12R	0	0	1	1	na	1	0	na	0	1	1	0	0	0	0	0	0	0	0	1	na	1
BA25L	0	0	0	0	na	0	0	na	0	0	0	0	0	0	0	0	0	0	0	0	na	0
BA25R	0	0	0	0	na	0	0	na	0	0	0	0	0	0	0	0	0	0	0	0	na	0
BA24L	0	1	0	0	na	1	0	na	0	0	0	1	0	1	1	0	0	0	1	1	na	1
BA24R	1	0	1	1	na	1	0	na	0	1	1	0	0	0	1	0	1	0	0	1	na	1

BA, Brodmann area; L, left; R, right; B, bilateral; and na, not available.

Table 3

Demographic data, basic cognitive, NPT and SST scores, and ANOVA *p* values for the FLD and NC groups (mean (*SD*))

	FLD	NC	ANOVA *p* values
N	15	15	
Age	61.4 (8.3)	61.9 (9.1)	.87
Education	15.7 (2.4)	16.0 (2.3)	.70
NPT			
Error rate	0.33 (0.4)	0.10 (0.1)	.07
Reaction times			
Control	846.1 (201.4)	600.2 (84.6)	.002*
DS	888.3 (240.9)	624.8 (95.6)	.005*
RD	875.5 (232.2)	608.1 (84.6)	.003*
TD	897.3 (279.9)	605.0 (94.0)	.006*
ND	823.1 (252.3)	546.2 (87.5)	.004*
Contrasts			
DS–C	42.3 (45.8)	24.6 (24.2)	.30
C–RD	−29.4 (64.3)	−7.8 (20.4)	.32
C–TD	−51.2 (97.9)	−4.7 (27.6)	.17
C–ND	23.0 (76.0)	54.0 (23.1)	.23
SST			
Mean RT	769.0 (135.4)	627.0 (132.9)	.010*
Accuracy	94.0 (6.0)	99.0 (0.5)	.004*
Probability	0.49 (0.02)	0.49 (0.01)	.94
Stop signal	266.7 (88.0)	212.8 (35.3)	.06
MDRS	117.5 (18.4)		
TOH	667.5 (507.4)		
WCST			
Categories	3.0 (2.8)		
% perseveration	33.8 (11.1)		
BDI	7.9 (11.1)		
Disease duration (years)	6.5 (3.2)		

DS, distractor suppression; C, control; RD, repeated distractor; TD, target to distractor; ND, no distractor; RT, response time. *p* values significant at the 0.05 level are marked with *.