

Frontal Brain Lesions Affect the Use of Advance Information During Response Planning

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This study examined the nature of the response programming deficit after frontal cortex lesions through the effects of advance information on sequence initiation time. Nine patients with unilateral frontal lesions, 9 patients with temporal lesions, and 9 controls performed a sequential key-press task involving 4 rapid choice responses to a 4-letter stimulus. Three conditions manipulated the number of responses that subjects knew in advance. The frontal group showed slow initiation times in all conditions. Knowing the first response produced an acceleration of initiation time in all 3 groups. However, knowing 3 responses in advance instead of 1 further accelerated initiation time in the control and temporal groups but not in the frontal group. These results indicate that frontal lesions impair the use of multiple representations during programming. This suggests that the attentional control of response selection is an important element of the response programming deficit.

There is now ample evidence that the frontal cortex has a significant role in the planning of actions. Patients with lesions invading the premotor cortex, prefrontal cortex, and/or anterior cingulate cortex experience difficulties in tasks with multiple steps such as complex problems (Della Malva, Stuss, D'Alton, & Willmer, 1993; Glosser & Goodglass, 1990; Shallice, 1982, 1991; Sirigu et al., 1996, 1998), maze performance (Canavan, 1983; Karnath & Wallech, 1992; Karnath, Wallech, & Zimmerman, 1991), and sequential movements (Canavan et al., 1989; Jason, 1985; Kolb & Milner, 1981; Lepage & Richer, 1996; Luria, 1969; Truelle et al., 1995). During the execution of sequential actions, frontal lesions can increase sequencing errors, omissions, and intrusions (Truelle et al.). In these studies, planning problems are generally inferred from problems observed after the initiation of responses.

The contribution of the frontal cortex in response planning can also be observed in recordings of cortical activity. Single-cell recording studies in nonhuman primates have shown that the prefrontal and premotor cortices are implicated in the preparation and execution of movement sequences (Barone & Joseph, 1989; Mushiaki, Inase, & Tanji, 1991; Passingham, 1993; Shima, Mushiaki, Saito, & Tanji, 1996; Tanji & Mushiaki, 1996; Tanji & Shima, 1994, 1996). In the supplementary motor cortex for example, some cells show an early premovement activation that is

specific to a certain order of movements (Tanji & Shima, 1994). Functional neuroimaging studies in humans have also reported an involvement of premotor regions in the preparation of simple motor responses (Deiber, Sadato, & Hallett, 1996; Lee, Chang, & Roh, 1999), whereas preparation of more complex motor activities such as reaching movements has been associated with activation in prefrontal regions (Decety, Kawashima, Gulyás, & Roland, 1992).

The role of the frontal cortex in response planning is still poorly understood. Planning is a complex activity that involves numerous processes such as the retrieval and coordination of representations about goals, rules, responses, and sensory consequences. Planning problems could arise from a variety of components of this control process. Deficits in complex tasks are especially difficult to interpret because they can be affected by many of these component processes. However, planning deficits can also be studied in simple tasks such as sequential responses. Patients with frontal lesions show a slowed execution of response sequences, or *bradykinesia*, and show execution errors at faster pace (Jason, 1986). In addition, we have shown that knowing responses in advance does not speed up interresponse time in these patients as it does in controls (Lepage & Richer, 1996). This acceleration effect of advance information is generally attributed to the added efficiency of being able to program future responses while execution of preceding responses takes place. The performance of patients with frontal lesions suggests that they have problems selecting a response while executing another. This concurrent-processing problem indicates that response selection or programming may be susceptible to attentional interference after frontal lesions. If response programming is limited by interference during sequence execution, this problem may also be present in the planning phase that precedes sequence initiation. The present study was designed to investigate whether the programming of sequential responses that occurs before initiation is also limited by interference after frontal cortex lesions.

The initiation of complex responses is often slow after frontal lesions (*akinesia*) but little is known about the variables that affect

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this initiation problem. In controls, sequence initiation time is affected by the complexity of response planning operationalized by the number of responses, their duration, or timing (Harrington & Haaland, 1987; Henry & Rogers, 1960; Inhoff, 1986; Kerr, 1978; Marteniuk & MacKenzie, 1980; Rosenbaum, Hindorff, & Munro, 1986; Sternberg, Monsell, Knoll, & Wright, 1978; Verwey, 1995; Zingale & Kowler, 1987). Sequence initiation time is also facilitated by advance information on the responses to be executed, at least for the first three responses (Rosenbaum, Hindorff, & Munro, 1987). Advance information allows preparatory processing of initial responses, which speeds up programming at the presentation of the imperative stimulus. Knowing in advance the first of four responses to execute has been shown to help initiate the sequence more rapidly, and knowing the first three responses further decreases initiation time. The present study examined the effect of advance information on initiation time after frontal lobe lesions in humans. Despite a slower initiation time, patients with frontal lesions should be able to facilitate programming (decrease initiation time) by preparing one response in advance. However, if their programming processes are subject to attentional interference, they may not be able to use advance information on multiple responses to further facilitate programming.

Method

Participants

Nine patients with unilateral frontal excisions (7 right, 2 left) were compared to 9 patients with unilateral temporal excisions (4 right, 5 left) and to 9 controls with no history of cerebral damage. Groups were matched in age (39 years, range = 25–56) and education level (11 years, range = 6–18). Except for 1 patient with a right frontal glioma (Patient 6, see Figure 1), all excisions were performed in adulthood to alleviate a drug-resistant epilepsy and patients were tested at least 2 years after the surgical intervention. Informed consent to participate in the study was obtained according to the rules of the institution.

Frontal excisions were variable in extent but always included dorsomedial structures (anterior cingulate gyrus and superior frontal gyrus, sometimes including the supplementary motor area [SMA]) and a variable amount of the dorsolateral cortex anterior to the precentral sulcus. Figure 1 shows the extent of the frontal resections. Seven of the patients with a frontal lesion showed a marked reduction in seizure frequency after surgery (80% or more), 2 were seizure-free, and all were on anticonvulsant medication. Except for Patient 3, all frontal patients were right-handed. Anterior temporal lobectomies involved resection of the anterior portion of the temporal lobe (about 5 cm from the anterior tip of the lobe), partial resection of the hippocampus, and sparing of Heschl's gyrus. All patients with a temporal lesion showed a marked reduction in seizure frequency (4 were seizure-free), and 6 were still on anticonvulsant medication. Eight of the temporal lobe patients were right-handed. All patients underwent postsurgery neurological and neuropsychological evaluation. None exhibited sensory or motor impairment or any hemispatial neglect on standard clinical measures. All patients had a Wechsler Adult Intelligence Scale IQ above 80 and could demonstrate comprehension and retention of task instructions. Neuropsychological evaluation revealed no significant deficits in language, episodic memory, or movement execution. Moreover, as shown in previous studies, frontal and temporal patients did not differ in control measures of rapid movements such as finger-tapping rate, simple reaction time, or two-choice reaction time (see Table 1).

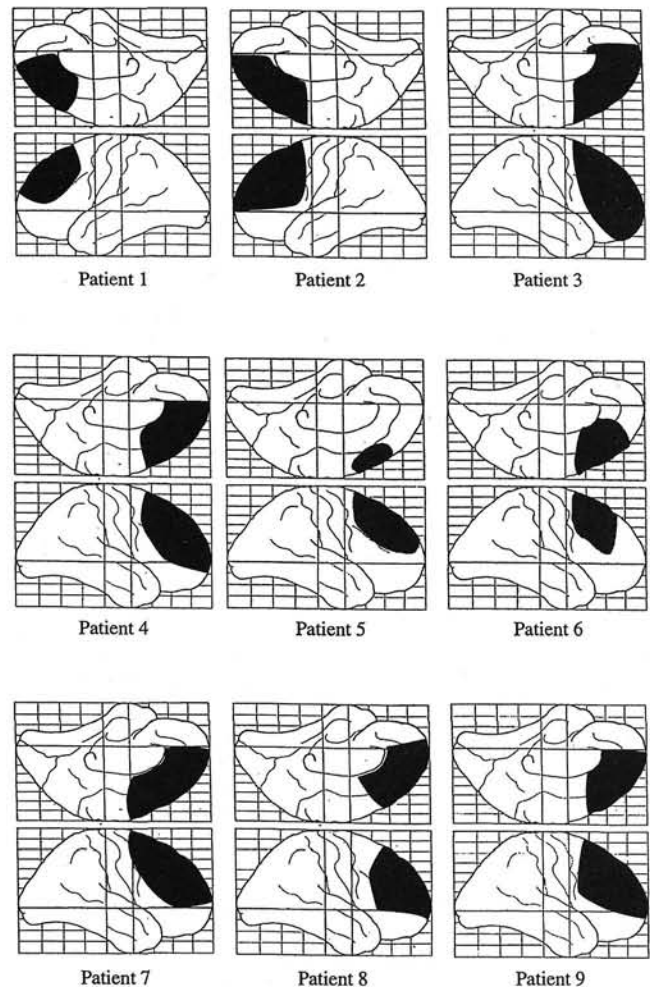


Figure 1. Schematic drawings of the extent of the frontal resections on lateral and medial views of the Talairach grid.

Tasks and Procedure

The experiment was controlled by a computer that ran Neuroscan software (Neurosoft, Sterling, VA). On each trial, participants were shown a stimulus composed of four capital letters presented simultaneously and were required to execute four rapid key-press responses (R1, R2, R3, R4). All letter sequences were composed of As, Bs, and Cs that were mapped to three adjacent buttons on a keypad. To make the number of sequence alternatives equal in all conditions, only three different letter sequences were presented in each condition. In one condition (R1–R3 unpredictable), the first three letters of the sequence were unpredictable and the last letter was always the same. The three sequences used in this condition were: ACBB, CBAB, and BACB. In the second condition (R1 known in advance), the first letter was identical from trial to trial (the letter B). The three sequences used in this condition were: BACB, BCBA, and BBAC. In the third condition (R1–R3 known in advance), the three first letters were identical from trial to trial and the following sequences were used: BCAA, BCAB, and BCAC. In each condition, one of the three sequences involved the immediate repetition of one letter, whereas the other two had no immediate repetition of a letter. Letters measured 1.2 cm wide \times 2.0 cm high and were presented in white against a black background, at a viewing distance of 60 cm. A trial consisted of the presentation of a fixation cross

Table 1
Group Means (\pm SD) of Control Measures
for the Two Patient Groups

Measure	Group		<i>p</i>
	Frontal	Temporal	
Simple reaction time (ms)	305 \pm 90	280 \pm 62	.30
2-choice reaction time (ms)	526 \pm 102	482 \pm 68	.20
Continuous tapping rate (per s)	5.2 \pm 1.2	4.5 \pm 1.0	.50

that was replaced after 1,500 ms by the sequence of letters, which remained on the screen until the end of the trial. An error tone was delivered whenever an error occurred.

Participants were instructed to respond as quickly and accurately as possible to each letter sequence. They responded by pressing three keys with the first three fingers of the dominant hand (index finger for A, middle finger for B, and ring finger for C), and a figure showing the associative rule between letters and keys was presented. In each condition, participants were presented with a figure showing the letters that would be identical in all trials; this figure remained in view during task performance. Comprehension of the instructions was verified by appropriate questioning before each condition.

The different conditions were presented in blocks to maximize the effect of the predictability of initial responses on initiation time. Participants were tested in four blocks of 20–30 trials, for a total of 100 trials per condition. The first block of each condition (20 trials) served as a practice block. Testing began with the condition involving R1–R3 known in advance, followed by the condition involving R1 known in advance. The third condition, R1–R3 unpredictable, randomly preceded or followed the two other conditions. The fixed order of the two conditions with responses known in advance was used to prevent practice effects from exaggerating the difference in initiation times between the conditions. Only correct sequences were examined in the chronometric analyses. Mean sequence initiation times were computed for the first response in the sequences (R1), and mean interresponse times were computed for the other three responses. Sequences with initiation times below 100 ms or above 2,500 ms were excluded from analyses. Successive trials were separated by 3 s, and a 30-s pause separated successive blocks.

Results

Performance Accuracy

The percentage of correct sequences completed by each group is summarized in Table 2. All groups showed generally good performance, but a high variability was found in the frontal group, especially in the condition with R1 known in advance. An analysis of variance (ANOVA) on the percentage of correct sequences showed a significant effect of group, $F(2, 24) = 4.20, p < .05$, but

Table 2
Mean Percentage (\pm SD) of Correctly Completed
Sequences in the Three Conditions

Condition	Frontal	Temporal	Control
R1–R3 unpredictable	79 \pm 11.6	88 \pm 6.1	93 \pm 5.1
R1 known in advance	84 \pm 16.3	89 \pm 9.3	92 \pm 8.7
R1–R3 known in advance	84 \pm 6.9	93 \pm 6.1	91 \pm 6.9

no significant effect of condition, $F(1, 24) = 0.20, ns$, or any significant interaction between group and condition, $F(2, 24) = .83, ns$. Contrasts revealed that the frontal group showed significantly lower accuracy compared with the control group (Tukey's honestly significant difference [HSD] = $-14.11, p < .01$) but not compared with the temporal group (Tukey's HSD = $-9.0, ns$).

Effect of Advance Information on Initiation Time

Because the main interest of the present study was the modulation of initiation time by advance information, initiation times (R1) were analyzed separately from interresponse intervals (R2–R4). Figure 2 depicts initiation times across the three conditions for each group. Initiation times were examined in two separate analyses that follow from the two a priori hypotheses, that is, (a) does the frontal group show a decrease in initiation time when initial responses are predictable compared with when they are not, and (b) does the frontal group show less facilitation when multiple responses are known in advance compared with when only one response is known (see introduction). A first analysis examined whether the presence of any predictable responses (1 or 3) at the beginning of a sequence decreased initiation time compared with the unpredictable sequence condition. Response times from both advance information conditions were pooled together and contrasted with the unpredictable sequence condition. The ANOVA showed a significant effect of advance information, $F(1, 24) = 63.04, p < .0001$, a significant group effect, $F(2, 24) = 16.42, p < .001$, but no significant interaction, $F(2, 24) = .98, ns$. The group effect was attributable to the general slowing of the frontal group, as post hoc analyses revealed significant differences between the frontal group and the two control groups on all three measures (all Tukey's HSDs ≥ 639 ms, $p < .001$). These analyses show that advance information speeds initiation time in all three groups.

Effect of the Number of Predictable Responses on Initiation Time

The second analysis of initiation time examined the effect of the number of predictable responses (one or three) at the beginning of the sequence. An ANOVA on the latency of R1 revealed a significant group effect, $F(2, 24) = 16.70, p < .001$, indicating a general

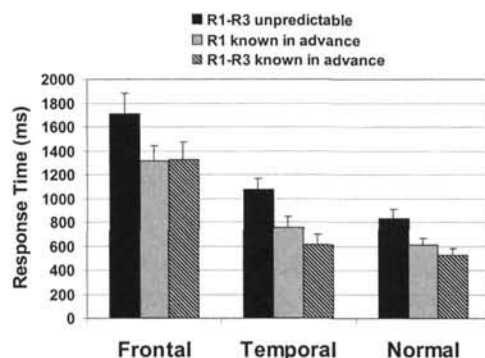


Figure 2. Mean sequence initiation times for the three conditions in each of the three groups. R = response.

slowing in the frontal group (all Tukey's HSDs ≥ 564 ms, $p < .001$), a significant effect of condition, $F(1, 24) = 9.50$, $p < .005$, and a significant interaction between group and condition, $F(2, 24) = 3.40$, $p < .05$. Simple effects revealed that the difference in sequence initiation time between the two conditions was significant for the control, $t(8) = 2.7$, $p < .03$, and temporal, $t(8) = 3.3$, $p < .01$, groups but was not significant for the frontal group, $t(8) = -0.2$, *ns*. Thus, in the control and temporal groups, sequence initiation time decreased as the number of predictable responses increased from one to three, but this acceleration was not detected in the frontal group.

Interresponse Time

Figure 3 depicts the mean interresponse times across the three conditions for each group. Separate ANOVAs were performed for R2, R3, and R4. For R2, the analysis revealed significant effects of group, $F(2, 48) = 6.18$, $p < .001$, again indicating a general slowing in the frontal group (all Tukey's HSDs ≥ 232 ms, $p < .002$); a significant effect of condition, $F(1, 24) = 11.85$, $p < .001$; and a significant interaction between group and condition $F(4, 48) = 3.71$, $p = .01$. Simple effects revealed that R2 latencies across the three conditions were not statistically different for the control group, $t(8) < 2.0$, *ns*, whereas in the temporal group, the unpredictable condition differed significantly from the advance information conditions, $t(8) > 3.2$, $p < .05$. In the frontal group, the fastest R2 was observed in the condition with one predictable response. This was significantly different from the other two conditions, $t(8) > 2.5$, $p < .05$, and there was no significant difference between the unpredictable condition and the condition with three predictable responses, $t(8) = 46.0$, *ns*. Analyses on the latencies of R3 and R4 revealed significant group effects, all $F_s(2, 24) > 14.90$, $p < .001$, but no significant effect of condition, all $F_s(2, 48) < 1.30$, *ns*, and no significant interaction, all $F_s(2, 48) < 1.06$, *ns*. Post hoc analyses on the group effect revealed that the frontal group was significantly slower than the two other groups (all Tukey's HSDs ≥ 255 ms, $p < .002$), but no difference was found between temporal and control groups (all Tukey's HSDs < 75 ms, *ns*).

Lesion Extent and Location in the Frontal Group

We examined individual differences within the frontal group and did not find any systematic differences in performance between patients with left frontal lesions (Patients 1 and 2) and patients with right frontal lesions. This could be attributable to our small sample size. However, it is clear from the present results and from other studies (Lepage et al., 1999; Lepage & Richer, 1996) that patients with a right frontal lesion can exhibit significant difficulties in response sequences. We also compared patients with lesions invading the SMA (Patients 2 and 7) to patients with more anterior lesions (Patients 1 and 8). Again, no obvious differences were observed. Finally, we examined the correlation between the size of the lesion and behavioral measures and did not observe any significant relation.

Discussion

This study examined the effects of frontal brain lesions on sequence initiation time. The present data suggest that frontal lesions (a) produce a general slowing of sequence initiation, (b) do not prevent the decrease in initiation time linked to advance knowledge of the first response, and (c) significantly reduce the facilitation of initiation time by advance knowledge of multiple responses.

Frontal brain lesions have long been known to produce a slowing in initiation (akinesia) and execution (bradykinesia) of complex movements (Heilman & Watson, 1991; Luria, 1969; Stuss & Benson, 1986), as have lesions in the striatum (Bhatia & Marsden, 1994). This slowing can be quantitatively assessed through initiation time and interresponse intervals in short response sequences. However, patients with frontal excisions can exhibit normal reaction time in simple responses even if they show slowing in more complex sensorimotor or cognitive tasks (Décary & Richer, 1995; Lepage et al., 1999). Thus, some of the processes that contribute to this slowing may be linked to the programming of more complex responses.

Advance information about the first response accelerated initiation in all groups, which suggests that it is possible to prepare a

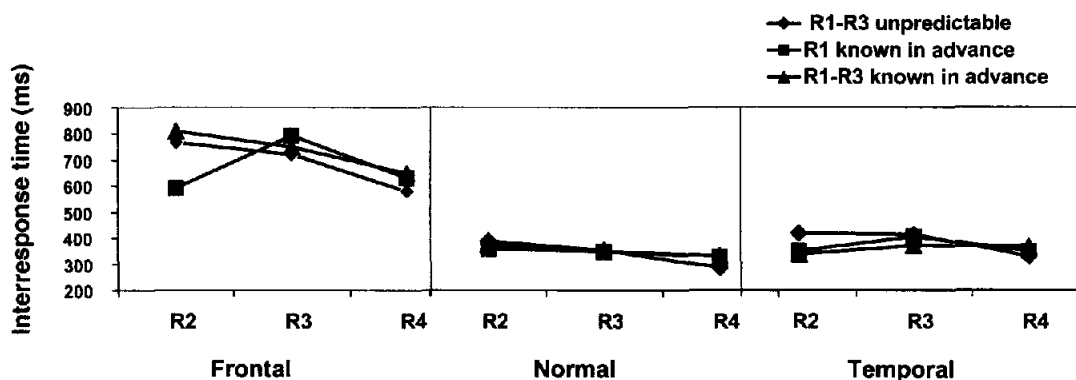


Figure 3. Mean interresponse times during sequence execution for the three conditions in each of the three groups. R = response.

single response after unilateral frontal lesions. Some studies have found that patients with frontal lesions do not benefit from advance directional cues indicating the location of a target to the same extent as patients with temporal lesions or controls (Alivisatos & Milner, 1989; Nagel-Leiby, Buchtel, & Welch, 1990). However, these tasks involved small delays between the advance information and the imperative stimulus as well as rapid spatial attentional shifts. In a mental rotation paradigm in which participants discriminated between normal and mirror-reversed characters, patients with a frontal lesion also showed a reduced effect of cue compared with patients with a temporal lesion (Alivisatos, 1992). In this task, the cue oriented attention toward some features of the imperative stimulus that could increase efficiency in response selection; frontal patients made less use of these partial features. In our sequence planning task, the first letter was provided in full, a minimal stimulus-response translation was required for response preparation, and long-term preparation could be used. These conditions may have minimized the cognitive demands of preparation in our task, producing large facilitation effects (> 200 ms) in all groups.

The critical result of this study is that the frontal group showed a reduced facilitation effect when three responses could be prepared in advance. One interpretation of this observation could be a floor effect. However, these patients can show faster response times in other key-press tasks (see Table 1). Another possibility is that frontal lesions cause a difficulty in learning the predictable stimuli or in maintaining them in working memory. However, the predictable letters were always in view, and all participants correctly recalled the three predictable letters before beginning the task. It thus appears that representations of the predictable letters were available to these patients. The problem appears to involve the use of these representations for selection or retrieval of the correct responses. This suggests that frontal lesions affect the extent to which programming can be facilitated by stored representations. A number of processes could disrupt this facilitation. The selection of multiple responses in close temporal contiguity challenges attentional control processes to prevent crosstalk during response selection or retrieval and to initiate each of the responses at the appropriate time (Allport, 1989). After frontal cortex lesions, representations of responses (motor working memory) may be more susceptible to interference by other representations or their retrieval may be slowed by competing representations. Whatever the mechanism, the present data suggest that part of the sequence programming limitation seen after frontal cortex lesions is due to interference between processes associated with different responses.

These data extend our previous observations of impaired advance information effects during sequence execution in patients with frontal lesions (Lepage & Richer, 1996). This problem with advance information during sequential responses has also been observed in patients with Huntington's disease (Bradshaw et al., 1992). Also, Richer, Bédard, Lepage, and Chouinard (1998) reported that rapid sequences of two responses are performed slower by patients with frontal lesions even when the responses are separated by 1 s. Taken together, these results suggest that, both before and after initiation, the programming of multiple responses is subject to attentional interference as a result of frontal brain lesions.

The present results cannot be specifically attributed to either premotor or prefrontal damage. Although much evidence points to an involvement of the premotor cortex in sequence initiation, there is evidence in the monkey literature suggesting that prefrontal regions also play a significant role in sequence programming and execution (e.g. Passingham, 1993). Also, in our sample, the presence or absence of damage to the SMA did not yield any significant differences in behavioral performance.

Many tasks that are sensitive to frontal cortex damage involve programming responses under attentional interference. For example, successful performance in complex problems or mazes (Canavan, 1983; Glosser & Goodglass, 1990; Karnath et al., 1991; Karnath & Wallech, 1992; Owen, Downes, Sahakian, Polkey, & Robbins, 1990; Shallice, 1982, 1991) requires that multiple moves be planned in advance. Self-ordered responses (Owen, Morris, Sahakian, Polkey, & Robbins, 1996; Petrides & Milner, 1982) also require the activation of past responses concurrently with the selection of future ones. Frontal lesions can also affect the simultaneous performance of two tasks (Baddeley, Della Sala, Papagno, & Spinnler, 1997). Frontal lesions in humans and monkeys can also cause problems in selecting single responses in novel contexts or when there is competition from prepotent responses (Décarry & Richer, 1995; Godefroy & Rousseaux, 1997; Halsband, 1987; Moll & Kuypers, 1977; Passingham, 1993; Petrides, 1990, 1997; Richer, Chouinard, & Rouleau, 1999). It is possible that sequential responses and responses in novel or competitive situations tax similar attentional control processes. Future research should be aimed at clarifying the links between the planning problems and other cognitive problems associated with frontal cortex lesions. The present data suggest that at least part of the planning problem observed after frontal lobe lesions may be attributable to an attentional control problem that limits the efficiency of response programming.

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Call for Nominations

The Publications and Communications Board has opened nominations for the editorships of *Journal of Applied Psychology*, *Journal of Consulting and Clinical Psychology*, *Journal of Educational Psychology*, *Psychological Bulletin*, and *Journal of Personality and Social Psychology: Interpersonal Relations and Group Processes* for the years 2003-2008. Kevin R. Murphy, PhD, Philip C. Kendall, PhD, Michael Pressley, PhD, Nancy Eisenberg, PhD, and Chester A. Insko, PhD, respectively, are the incumbent editors.

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