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Event-Related Potential Components N1, P2 and P3 to Rare and Frequent Stimuli in Intellectually Impaired Neurological Patients

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Summary. Event-related potentials (ERPs) and attention performance data were collected in an auditory oddball paradigm from 24 intellectually impaired neurological patients, and compared with normal controls ($n = 19$). For the ERP components N1, P2 and P3, reference-independent measures (latency, global field power, current density at Cz, location of extreme potential, centroid location) were determined for the target stimulus and for the preceding and the following two "frequent" stimuli. In 8 of the 45 measures obtained, patients and controls differed significantly. To target stimuli, patients had shorter N1 latency and smaller current density, more posterior P2 location and longer P3 latency; to immediately following "frequent" stimuli, longer P2 latency; and to preceding and both following "frequent" stimuli, smaller P2 current density. Attention performance was significantly worse for the 15 patients who scored on at least one of the eight ERP measures above normal range than for the other 9 patients. Decreased N1 latency to targets is viewed as failure to activate normal attentional capacity; changed P2 location suggests activation of deviant neuronal populations in response to targets; and increased post-target P2 latency suggests abnormal persistence of induced state change.

Key words: ERP oddball paradigm – Serial order of frequent stimuli – Brain damage – Spatial ERP analysis – Intellectual impairment

Introduction

Event-related brain potentials (ERPs) can be elicited in the so-called oddball paradigm, using attended tone stimuli which rarely and randomly occur in a series of unattended and frequent stimuli of different pitch. The ERPs in this paradigm (e.g. Picton and Hillyard 1974; Pfefferbaum et al. 1984a) reportedly differ between normals and psychiatric and neurological patients of various aetiologies (e.g. Pfefferbaum 1984b; Goodin and Aminoff 1986; Gummow et al. 1986; Coffman and Torello 1989; Goodin 1990; Ito et al. 1990; Polich et al. 1990; but see Slaets and Fortgans 1984 for contradictory results). Typically, the component P3 is measured, a positive centroparietal wave at about 300 ms after the rare stimulus; consistently, increased latency and reduced amplitude of P3 elicited by the rare stimulus was found in patients, but diagnostic usefulness is low because of the large variances (Pfefferbaum et al. 1984b; Polich et al. 1990). Earlier ERP components such as N1 (negative around 100 ms) or P2 (positive around 200 ms) have received little attention in clinical applications, because it had been frequently assumed that these components do not reflect attentional processes; however, some reports have indicated the opposite (e.g. Picton and Hillyard 1974; Roth et al. 1976; Polich et al. 1990).

Recently, we studied changes of the ERPs that are produced by the time relations between the frequent stimuli and the rare stimulus during the oddball paradigm in normal subjects (Hirata and Lehmann 1989). Significant differences existed between various measures of the N1 and P2 components elicited by the frequent stimuli before and after a rare stimulus. Some of these measures might be useful for clinical diagnosis.

In the present study we tested the clinical usefulness of these measurements in a group of demented neurological patients.

Patients and Methods

Twenty-four inpatients (17 males, 7 females) of the Department of Neurology, University Hospital Zurich were examined (mean age 53.8 years, SD 13.8). The patients were sequential referrals to the laboratory. The only selection criteria were the clinical diagnosis of impairment of intellectual functions due to brain damage, and the ability and willingness to comply with the counting task for the "oddball paradigm". Eleven patients had been diagnosed as having cerebrovascular disease, 5 brain tumours, 4 hydrocephalus, 2 alcohol abuse, and 2 were after head trauma. Four other referred patients were unable to count the rare pips ($n = 2$) or could not sit quietly ($n = 2$) and were therefore omitted from the analysis. Nineteen right-handed, healthy volunteers (mean age 48.4 years, SD 16.7; 13 males, 6 females) served as controls.

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The subjects were instructed about the task. Gold-plated Grass electrodes were attached with Grass EC-2 paste at Fz, Cz and Pz. These three midline locations cover the area of occurrence of the negative peak of component N1 and of the positive peaks of components P2 and P3, as illustrated in Fig. 1. Ear electrodes combined via 10 kΩ resistors were the recording reference. An additional channel monitored eye movements from electrodes above and below the left eye. The subjects were seated in a sound- and light-shielded chamber in a comfortable chair facing a loudspeaker. An intercom system connected subject chamber and recording room. The subjects were told to keep their eyes closed during the recordings. Two patients who could not keep their eyes closed without repetitive twitching were asked to fixate on a mark on the wall of the dimly lit chamber. The subjects were asked to count the rare stimuli silently. Then, a trial run was done to familiarize the subject with the procedure.

The tone pips were presented at 700-ms intervals, using 2000 Hz for the frequent tones and 1250 Hz for the rare tones, at 85 dB SPL. Fifteen percent of all tones were rare, randomly replacing a frequent tone, but after a rare tone, at least 3 frequent tones were presented. The tone pips were presented in runs with 22–24 rare tones each, each run lasting about 2.5 min. After each run, the subject was asked to report the number of rare tones; the subject was thanked, but no feedback about errors was given. Four runs were recorded at 4.5 min intervals. On the average, it was possible to record 3.1 runs only. Averaging was started after the occurrence of the second rare tone for the 20 following rare stimuli.

The number of target tone counts reported by the patient was computed as the percentage deviation from the number of actually presented target tones (called "target error percentage").

After the electric recordings, the patients underwent the continuous performance test (CPT, Rosvold 1956) in an auditory version. During 7 min, the patients listened to a series of 325 randomly chosen combinations of two letters at about 1.3-s intervals. They had to count all cases of the combination *"ax"* (there were 60). The number of counts below or above correct was noted as CPT "count error".

The EEG signals were amplified, recorded on FM tape, and played back on-line to a strip chart recorder for monitoring. Using a Nicolet 1172 analog-to-digital conversion averaging was done off-line from the FM tape recording after analog band passing via Krohn-Hite filters (1–30 Hz, 3 db down with 18 db/octave). The averaging ($n = 20$) epoch started with the frequent tone (called "$x-1$") immediately preceding the rare tone (called "x"), and ended 2800 ms later after the first two post-target frequent tones (called "$x+1$" and "$x+2$"), as shown in Fig. 2; 512 data points were available for the 2800 ms epoch. Because of the numerous artefacts in the patient records, averaging was done off-line from tape for patients after hand-editing of eye movements and other artefacts; for normals, on-line averaging was done, using the artefact rejection of the Nicolet (eye channel signals larger than 50 μV). The baselines were measured by short-circuiting the preamp inputs and performing the regular averaging procedure; baseline values accordingly represent a completely flat field distribution. All averaged data were transferred to an LSI11/23 computer for further treatment.

The three components N1, P2, and P3 were measured. Five reference-independent non-ambiguous parameters were used which do not privilege any single location (Lehmann 1987; Lehmann et al. 1977; Lehmann and Skrandies 1979, 1980). The *latency* of a component was defined as the time of the maximal potential difference from baseline (i.e. from flat field) between any of the four electrode locations Fz, Cz, Pz and "ears". The latencies of the N1 and P2 components for all four stimuli were determined within two pre-set time windows: for a negative extreme value between 65 and 135 ms latency, and for a positive extreme value between 140 and 240 ms. For the rare stimulus x, an additional window between 250 and 500 ms latency was searched for a positive extreme (P300). Thus, nine latencies were obtained for each run. At each of these latencies, the voltage vs baseline was measured in all three channels; these 27 amplitudes were further analysed.

The one-dimensional *current source density at Cz* (Skrandies 1987) was computed as one characteristic of the strength and spatial distribution of the brain field, using the three available scalp locations; this yields the in- or outgoing current at Cz. Current source density at Cz was computed as the sum of the voltages at Fz and Pz minus twice the voltage at Cz. The result is positive for a current source, negative for a sink. As a direct assessment of the spatial distribution of the components we obtained at the determined latencies the *location of the maximal potential* value in the momentary potential profile over the three midline electrodes.

The parameter *component strength,* assessed as the value of global field power at component latency (Lehmann and Skrandies 1980; Pfefferbaum et al. 1984a), did not show significant differences between patients and normals as groups, in line with the usual disappointing results of component amplitude measures in clinical practice. Likewise, the parameter *location of the centroid* of the potential profile, which was of interest in a study on normals (Hirata and Lehmann 1989), did not show differences between patients and controls.

For the exploratory statistics, unpaired *t*-tests were used to compare the patient and the control group data, and paired Wilcoxon tests to compare patient data obtained with different stimuli.

Results

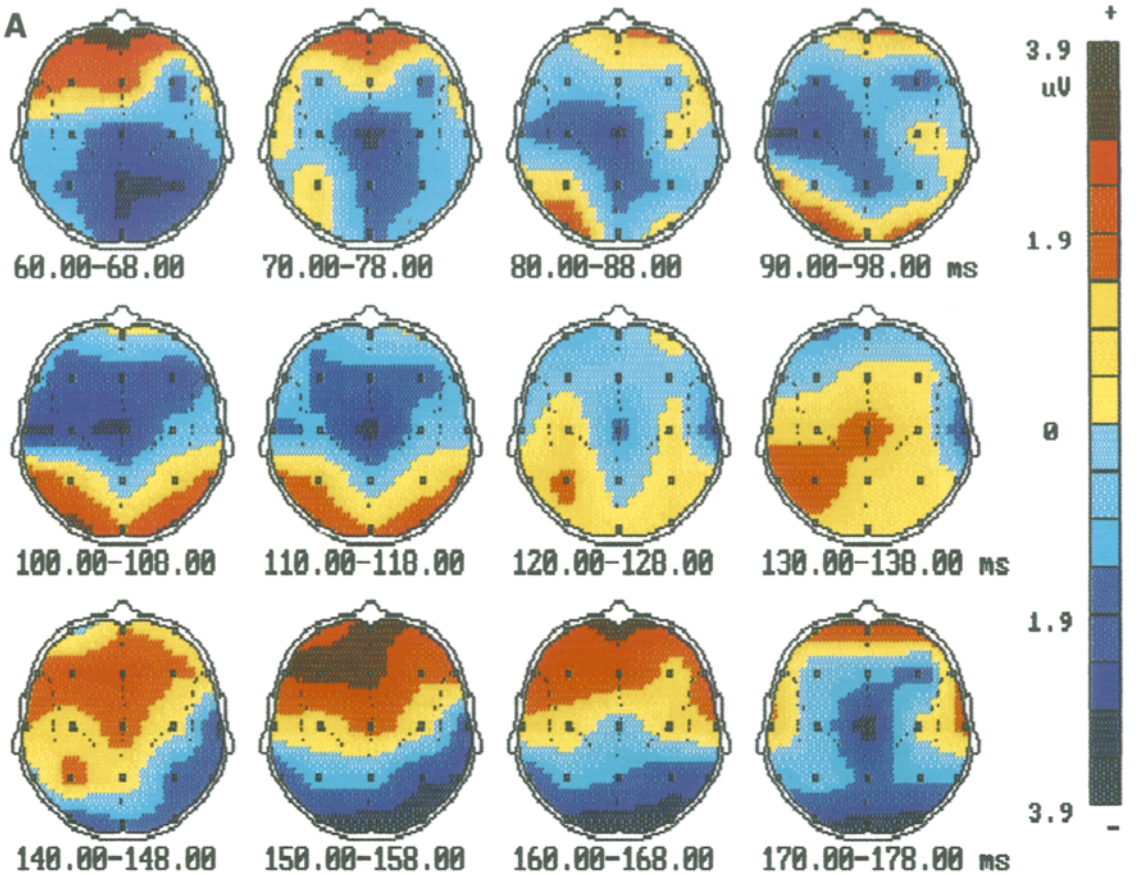
The statistical comparisons between patients and normals yielded significant differences in three of the five parameters, on 8 of the 45 measures: latency of N1, P2 and P3, current source density of N1 and P2 (for three stimuli), and location of maximal potential of P2. The results obtained with the three relevant parameters are shown in Fig. 3.

Four of the significant differences concerned the ERPs to the target: the patients had shorter latencies for N1 and longer latencies for P3, smaller current source density for N1, and a more posterior location of P2. The other three significant differences concerned non-target P2 measures: the patients showed increased latency at $x+1$, and decreased current source density at $x-1$, $x+1$ and $x+2$.

Testing the patient data for differences between pre-target and target, only the location of P2 showed a significant change: it had moved posteriorly. Post-target ERPs differed from target ERPs in that N1 latency at $x+2$ was significantly shorter than at $x-1$, x and $x+1$, and current source density was smaller at $x+1$ than at $x-1$.

With regard to performance measures, the mean target error percentage of the 24 patients was 21.5 (SD 43.0; median 5; range 0–186). The mean CPT count error result of the patients was 5.04 (SD 8.13; median 2; range 0–35).

We examined the relationship between the eight ERP measures which had shown significant differences and the two performance measures. The two performance measures were summed for each patient; we then determined how many of the eight relevant ERP measures of each patient fell beyond the range of the normals. Nine patients had all eight measures within the normal range, 6 scored outside in one, 5 in two, and 4 in three of the eight ERP measures. We tested the median of the summed performance measures of the 9 patients whose eight ERP measures were within the normal range (median 5) vs that of the 15 patients with any of the eight ERP measures beyond the normal range (median 21); the perfor-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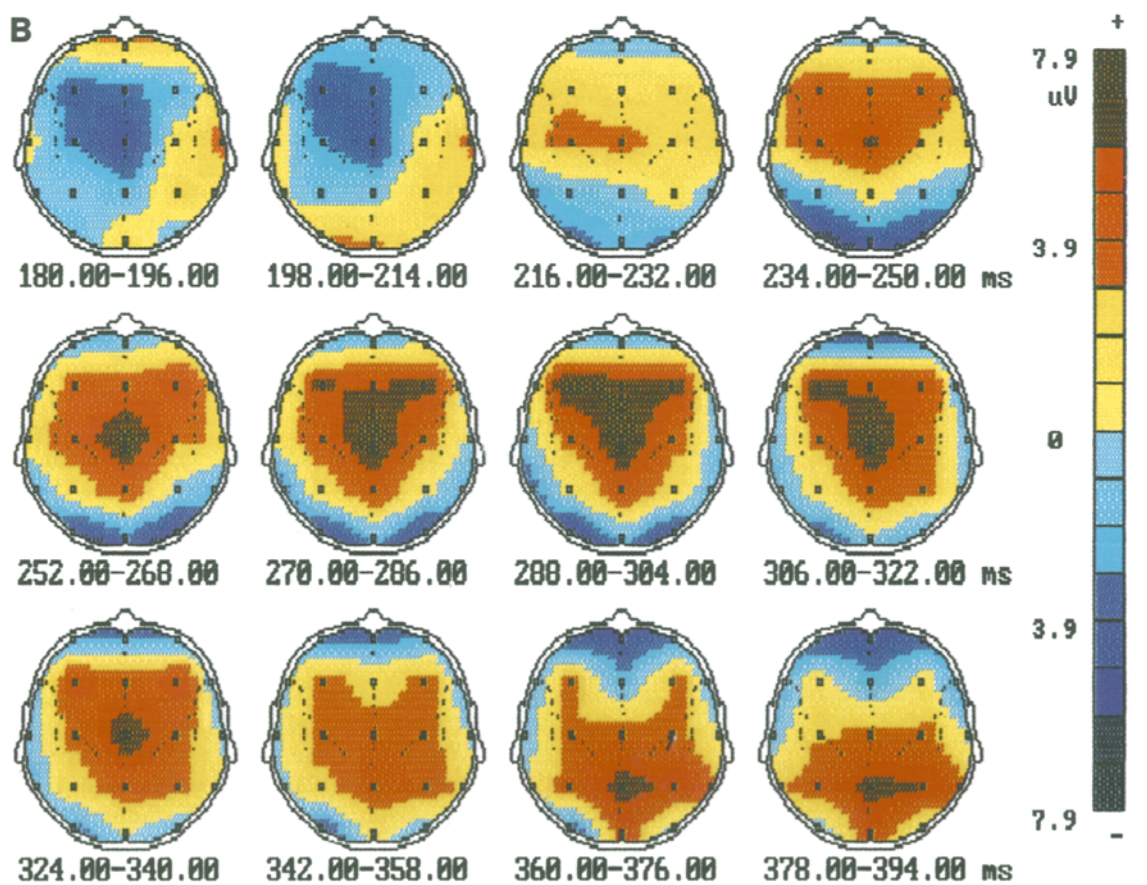
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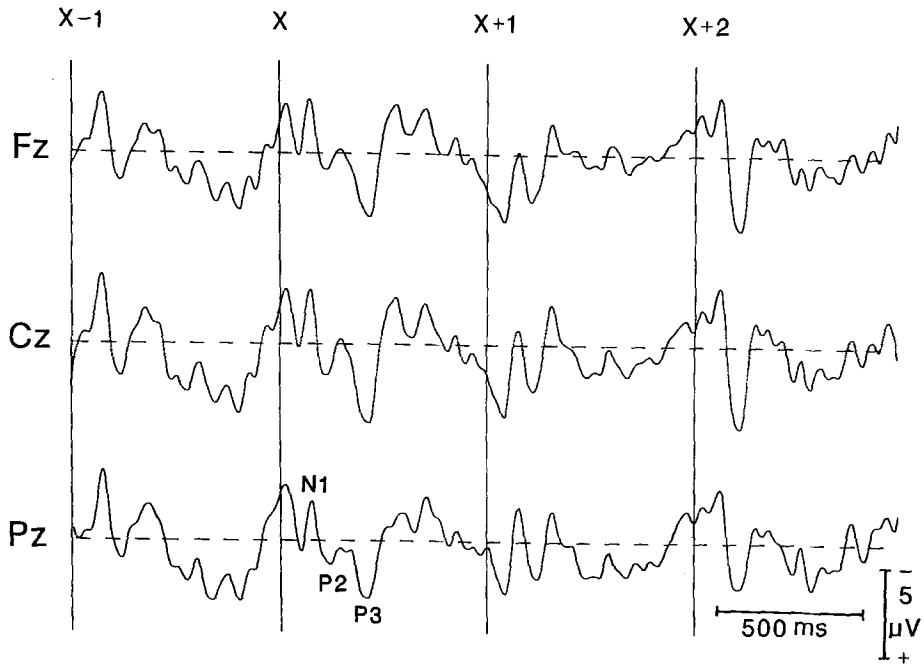

Fig. 2. Example of data collected in one run. Averaged event-related potentials ($n = 20$) to the rare target stimulus *(x)* and the preceding ($x-1$) and the following two ($x+1$, $x+2$) frequent stimuli *(vertical lines)*, from the three electrode combinations Fz, Cz and Pz against combined ears. *Dashed line* (measurement zero) indicates zero potential difference between scalp electrodes and reference. Positivity down

mance differed significantly between these two patient groups (U test $P < 0.025$). When only P3 mean latency and P3 latency range were used as classifiers for the two groups (18 patients were "normal"), there was no significant difference in performance between the groups.

Discussion

Summarizing the results in the patients we observe that in addition to abnormal P3 characteristics to target stimuli, there are also abnormal N1 and P2 characteristics to target stimuli, and persisting effects to non-target simuli.

The target-related ERP abnormalities are interesting in three respects. Firstly, the location of the target P2 more posterior than the pre-target P2 is contrary to the normal result (an anterior move) (Hirata and Lehmann 1989) and results in P2 being more posterior in patients than normals. This implies that the abnormal ERP involves a neuronal population which must be different from the normally activated population, and also different from that which is activated by the frequent pre-target stimulus. The more posterior P2 in our patients is reminiscent of observations on posteriorization of P3 in dementia (Mita et al. 1983; Pfefferbaum et al. 1984b); however, this was not convincing in our current data, conceivably because of the larger inter-electrode distances, which reduced spatial resolution.

Fig. 1A, B. Example of an event-related map series. Sequence of momentary scalp potential distribution maps, summed over the indicated times after the occurrence of the rare target tone in a normal 30 years old subject. Average of 20 stimuli. Twenty-one channel-maps (BioLogic Brain Atlas) recomputed vs the average reference. (This procedure does not change the maps' landscapes.) *Blue*, Negative; *yellow/red*, positive; 10/20 electrode placements. Note different summing epochs and different colour/voltage ranges (different calibrations, on the *right*) in **A** and **B**; this is necessary because of the slower changes of the landscape and the larger amplitudes at later times. Head seen from above, nose up

Secondly, the patients had shortend N1 latency to target stimuli. In normals, there is a latency increase for the target-evoked N1 compared with the pre-target-evoked N1 (Hirata and Lehmann 1989), which in view of the reports in the literature (Roth et al. 1976) was felt to manifest increased processing efforts. Accordingly the absence of latency increase for N1 suggests a deficit of attentional effort. On the other hand, the slowing of the P3 latency is in agreement with many reports on oddball ERPs in various groups of psychiatric patients (Pfefferbaum et al. 1984b; Roth et al. 1980) and neurological patients with cognitive and attentional disturbances (Hansch et al. 1982; Gummow et al. 1986; Ball et al. 1989; Ito et al. 1990; Polich et al. 1990). N1 and P3 latencies thus show opposing trends in disturbed intellectual functions.

Thirdly, the reduced strength (current source density) of our patients' N1 to targets agrees with the reduced N1 and P2 amplitude in CVA (Gummow et al. 1986) and dementia (St. Claire et al. 1985; Polich et al. 1990). It is compatible with the concept of reduced attentional activation, but we note that it must concern relatively early stages of information processing, earlier than 100 ms after information arrival.

Most of the abnormal post-target ERP persistence of target effects in patients concerns the current source density data. A simple explanation might be a generally lower response strength, numerically apparent, but not significant in all cases. On the other hand, the patients' P2 latency was longer than normal P2 latency $x+1$, possibly another abnormal non-target persistence of a target effect. [Polich et al. (1990) reported prolonged non-target P2 latency in dementia.]

In the present study, we examined 45 non-ambiguous measurements of ERPs to target and non-target stimuli in intellectually impaired neurological patients. Eight of these functional ERP measures yielded significant differences from the norm in exploratory statistics. An attempt to recognize the patients by using only the normal range

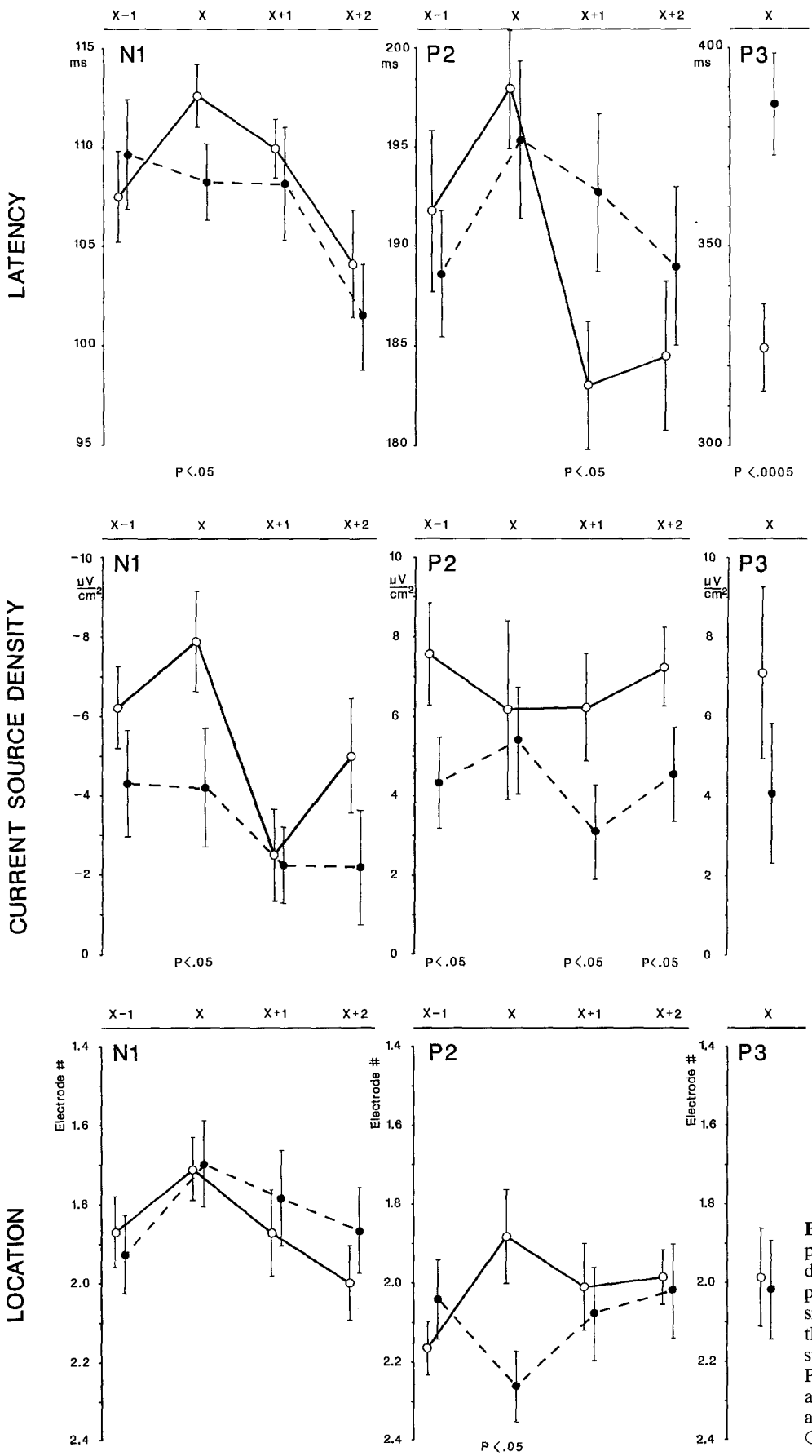

Fig. 3. Results of the measurement parameters: latency, current source density at Cz, and location of maximal potential; means, standard errors and significances of differences ($P < 0.05$) for the 24 patients and the 19 control subjects, for the components N1, P2 and P3 and the stimuli $x-1$, x (target), $x+1$ and $x+2$. For "Location": electrode 1 was at Fz, electrode 2 at Cz, electrode 3 at Pz. ○——○, controls; ●---●, patients

of P3 latency as identifier led to 6 of the 24 being diagnosed as pathological cases, whereas 15 of the 24 were classed as pathological cases using the normal ranges of all the eight significant measures as identifiers (the difference between the two treatments was significant; $P < 0.01$ in Fischer's exact test). When using the mean + 3 SD of P3 latency as the cut-off, 15 pathological diagnoses likewise resulted in the 24 paitents, but 1 of the 19 normal controls was now diagnosed as pathological – a false-positive result, which should be avoided in laboratory tests. While the larger battery's greater yield is not very surprising, it is interesting that – in contrast to P3 latency alone – the combined scores of the eight measures reflected the severity of the deficit as defined by performance (event counting), supporting other ERP-to-performance correlations in patients (e.g. Polich et al. 1986).

Although we obtained an encouraging diagnostic result with our eight ERP measures, we are only mildly optimistic about clinical routine applications in the near future, since (besides questions of diagnostic reliability and specificity; see Pfefferbaum et al. 1990) the procedure is quite demanding for patients and experimentors: an appreciable fraction of our referred patients were simply unable to cooperate adequately in the examination (4 of 28), and considerable work is necessary to edit out numerous eye, mouth and body movement artefacts, which in older intellectually impaired patients are unavoidable.

In summary, utilization of sets of measurements of the oddball paradigm ERPs continues to promise physiological statements about the presence and severity of intellectual deficits, and might possibly lead to an improvement of the insufficient clinical usefulness of ERPs in this field (Pfefferbaum et al. 1984b; Polich et al. 1990); in fact, encouraging results were obtained with one measure only if the diagnostic question was restricted (differentiation between two groups: Brown et al. 1982; Gordon et al. 1986; between three groups: Goodin and Aminoff 1986).

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