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Quantitative analysis of hemispatial neglect in the intracarotid sodium amobarbital (ISA) test

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Abstract

There are dramatic changes in the electroencephalogram of the inactivated hemisphere in the intracarotid sodium amobarbital test. One of the more profound behavioral changes during this procedure is left hemispatial neglect accompanying right hemisphere inactivation. The present study was designed to ascertain whether there was a clear relationship between the degree of hemispheric inactivation (as measured by the electroencephalogram) and the degree of left hemispatial neglect during this procedure. Sixty-nine participants undergoing right hemisphere intracarotid sodium amobarbital testing were presented with a random letter cancellation test at various points during the procedure. Neglect was quantified as *significant*, *moderate*, *minimal*, or *none*, based on how many target letters the patients missed. The simultaneous electroencephalogram from each of these testing points was spectrally analyzed and topographic maps were generated. The degree of neglect was then compared with the comparable topographic map. It was found that as the amobarbital-induced right hemispheric dysfunction regressed, the degree of neglect lessened in a systematic fashion, as did the profound electroencephalographic changes induced by the drug. Thus, there is a clear relation between the degree of hemispheric inactivation induced by the amobarbital and the degree of left hemispatial neglect. This relationship held regardless of side of hemispheric language dominance or epileptic focus. These results replicate previous findings that right hemisphere inactivation during the intracarotid sodium amobarbital test results in left hemispatial neglect. They extend these findings by clearly showing that neglect changes in a quantitative fashion (rather than being an all-or-none phenomenon) and further, show that there is a clear relationship between the severity of neglect and the degree of hemispheric dysfunction. (*JINS*, 1998, *4*, 99–105.)

Keywords: Amobarbital, Epilepsy, ISA, Neglect, Quantitative EEG, Wada Test

INTRODUCTION

Neglect of contralateral personal or extrapersonal space is usually associated with (and is more profound in) lesions of the right hemisphere (Heilman et al., 1993; Mesulam, 1981). A number of different behavioral types of neglect may been seen, including sensory–perceptual, motor–intentional, motivational, etc. In an analogous fashion, a number of different lesion sites in the right hemisphere have been identified, including parietal (Denny-Brown & Chambers, 1958) and frontal lobes (Heilman & Valenstein, 1972), insula (Berthier et al., 1987), internal capsule (Ferro & Kertesz, 1984), basal ganglia (Healton et al., 1982), and thalamus (Watson & Heilman, 1979). In order to relate these various types of neglect and the multiple lesion sites capable of producing them, a number of authors have postulated the existence of a widely distributed network for spatially distributed attention (Heilman et al., 1993; Mesulam, 1985, 1990).

The intracarotid sodium amobarbital (ISA) or Wada test is performed in patients for whom surgical intervention is indicated to treat medically intractable epilepsy (Loring et al., 1992; Wada & Rasmussen, 1960). The goal of this

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procedure is to evaluate language dominance and memory performance prior to surgery. Sequential and transient inactivation of each hemisphere is accomplished *via* infusion of sodium amobarbital into the internal carotid artery (ICA).

A number of studies have examined neglect and/or related phenomena during the ISA. Meador et al. (1988) found that on both single and double simultaneous stimulation tasks, tactile inattention and extinction occurred more frequently during right ISA. They also found evidence of allochiria during right ISA (i.e., left-sided touches eliciting right-sided responses), but not during left ISA. Spiers et al. (1990) documented a disturbance of visuomotor scanning on a random letter cancellation test (RLCT), characterized by contralateral neglect during right, but not left, hemispheric inactivation. This relationship held not only for right-handed patients with left hemisphere language dominance, but for left-handed patients and right hemisphere language dominant patients as well; side of epileptic focus was also found not to affect the results. The electroencephalogram (EEG) was recorded during these ISAs. It was subsequently scored visually. It was found that the left hemispatial neglect correlated most strongly with slowing in the right frontal lobe. Manoach et al. (1996) found that while 10 of 16 participants demonstrated left hemispatial neglect on the RLCT, only 1 of 16 showed left neglect of a remembered scene (a familiar room in their house). Thus, they concluded that ISA-induced neglect of visuomotor scanning could be dissociated from neglect for mental representations. They suggested that this might be due to a greater degree of hemispheric inactivation in anterior (as compared to posterior) regions during the ISA.

One goal of the present study was to determine whether the degree of left hemispatial neglect seen during the right ISA changed over time, in accordance with decreasing amobarbital effect, or whether this was an all-or-none phenomenon. Another goal was to extend the work of Spiers et al. (1990) through the utilization of EEG spectral analysis and topographic mapping. The EEG analysis performed therein was based on bipolar montages, which might have underestimated the degree of change in the EEG during the ISA because of common mode rejection between adjacent electrode pairs. If this were the case, then the correlations between the degree of neglect and the EEG might also underestimate the true relation(s). Prior work by the current group (Ahern et al., 1994, 1995) had described the profound changes that occur in the EEG following induction of hemispheric anesthesia during the ISA. We wanted to ascertain whether these changes correlated with the degree of left hemispatial neglect (were the latter to be a quantitative phenomenon).

METHODS AND MATERIALS

Research Participants

Sixty-nine consecutive patients undergoing the ISA procedure in whom the EEG was acquired and stored, constituted the participant pool. Pertinent demographic characteristics were: mean age = 32.7 years (range: 13–65); 34 male/35 female; 55 right-handed/13 left-handed/1 ambidextrous. Language dominance for any particular patient was determined based upon the presence (during the ISAs) of such factors as speech arrest immediately following injection, abnormal performance on tasks of comprehension, repetition, and naming, and the presence of semantic and/or literal paraphasic errors. Fifty-seven patients were unequivocally left-dominant for language, while 3 were clearly right-dominant; of the remaining 9 patients, 3 were left > right, 4 were right > left, and 2 were equally dominant for language. (Patients were not excluded for being non-left-hemisphere dominant for language, as all patients showed left hemispatial neglect regardless of language dominance. Furthermore, the study of Spiers et al. (1990) suggested that left hemispatial neglect occurred during the right ISA regardless of language dominance.) Thirty-three patients had epileptic foci and/or lesions in the left hemisphere, 35 in the right hemisphere, and 1 had bilateral pathology.

Procedures

Informed consent for the ISA and all procedures performed therein was obtained from each patient. All patients had arteriograms prior to the ISA. Sodium amobarbital was injected into the ICA by slow hand injection, the average dose for the right hemisphere ISA being 114.3 mg (range: 60–200). Injection order varied between participants, as the usual case was to perform the ISA on the abnormal hemisphere first. In 39 participants, the injection order was right hemisphere followed by left hemisphere. These injections were separated by a period of not less than 30 min in order to allow the amobarbital from the first injection to be cleared from the system.

Random Letter Cancellation Test

Figure 1 shows the random letter cancellation test used with all participants. This measured 24 × 18.5 cm and consisted of 36 target letters ("A") and 96 distractor letters ("B," "H," "K," "R") randomly distributed throughout the field, but with a general symmetry in each of the four quadrants. During testing, this form was held in front of the patient's face at arm's length (approximately 36 cm) and was moved as necessary to keep it centered with respect to the participant's nose. The patients were instructed to point (with the right hand) to as many "A"s as they could find. This generally took 30 s or less to do. They were allowed to continue as long as they were making progress in the horizontal plane; if the patient got "stuck," that is, kept pointing to targets in the same zone, the test was discontinued. The initial presentation of the test was performed during the early phase of the right hemisphere ISA, generally within the first 2 to 4 min. (Even patients who became aphasic during right ISA, were able to be tested within this time window, as receptive

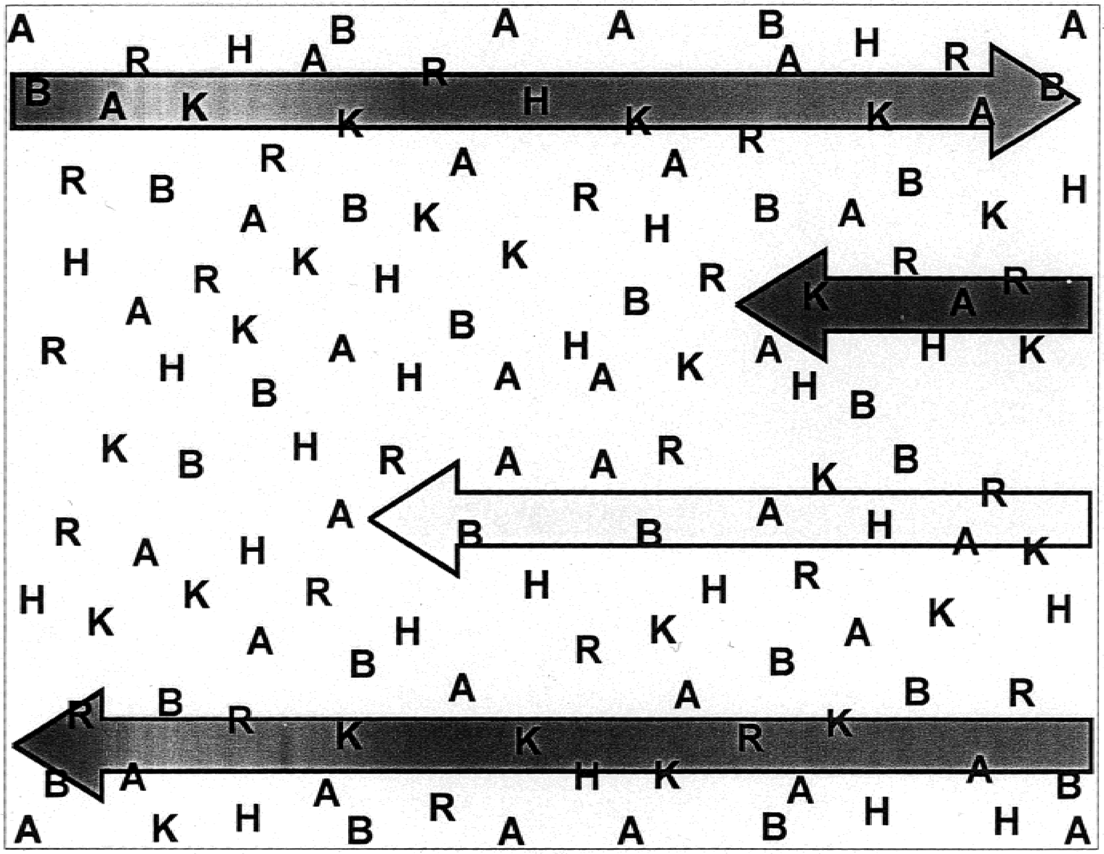
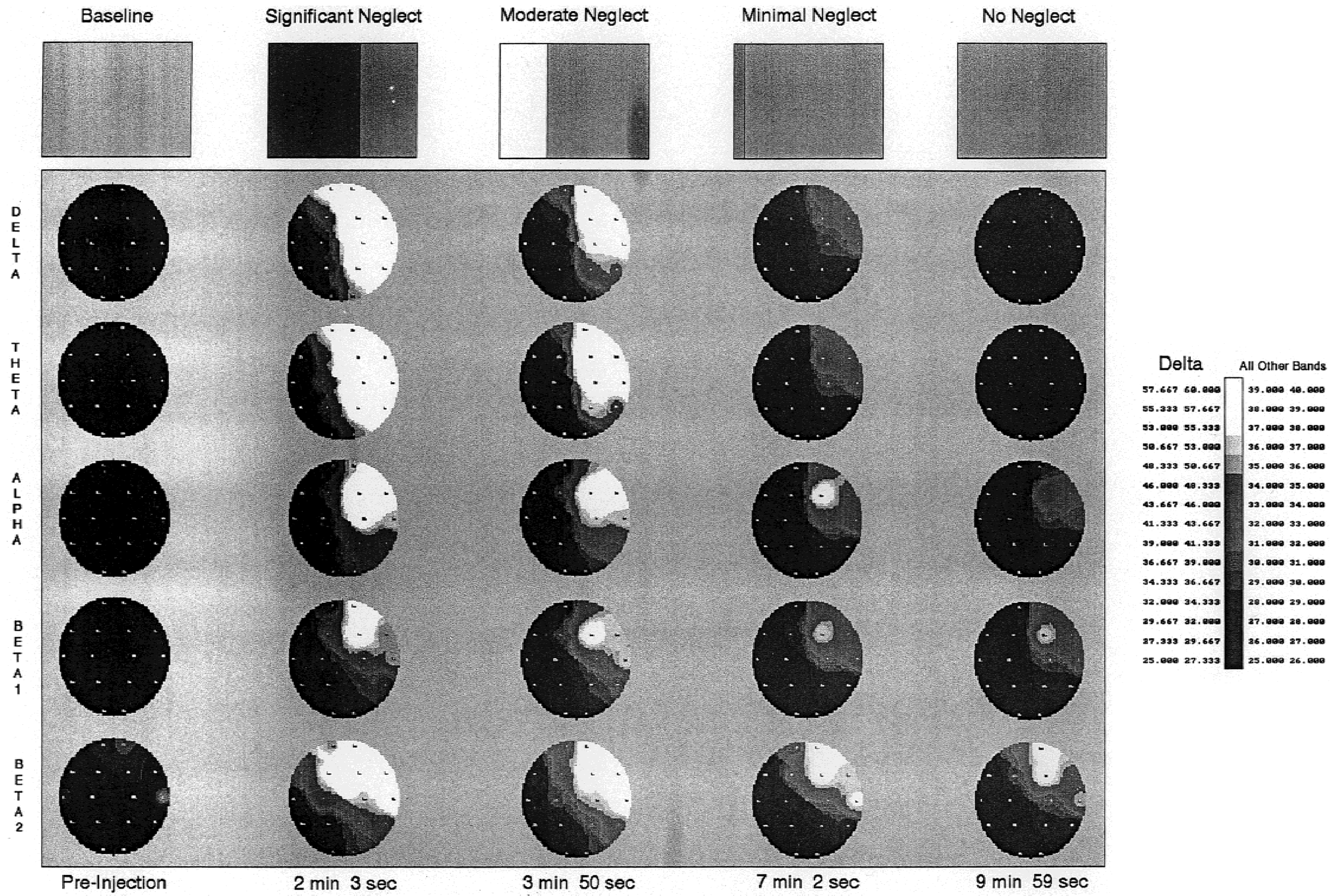


Fig. 1. The random letter cancellation test used in the current study. Superimposed on this are colored arrows denoting the visuospatial extent of target letter "A"s detected under varying conditions of neglect. The blue arrow reflects the *normal* (or no neglect) condition, in which patients detect targets in all quadrants and furthermore, scan from left to right. The red arrow denotes *significant* left hemispatial neglect; patients acquire targets only in the right 1/3 of space (neglecting the left 2/3), and furthermore, scan from right to left. The yellow arrow denotes *moderate* left hemispatial neglect; patients acquire targets only in the right 2/3 of space (neglecting the left 1/3). The green arrow denotes *minimal* left hemispatial neglect; patients neglect targets only in the extreme left side of the page, but still scan from right to left.

language had recovered enough that they were able to follow the instructions.) When possible, a second and possibly even, third or fourth, presentation was made later on. The test was not presented if there was clinical evidence of an actual left visual field cut (anticipated based on data from the preceding angiogram suggesting that the right posterior cerebral artery territory was filled from the ICA).

Each patient's ISA videotape was reviewed and the degree of neglect (and the time of any particular trial) was quantified in the following way. A normal performance was

Fig. 2. (*facing page*) Differing degrees of neglect and the corresponding EEG topographic maps occurring during the right hemisphere ISA. Parts of the random letter cancellation test (top) colored blue reflect areas in which targets are accurately perceived. Zones colored red, yellow, and green reflect areas neglected under conditions of *significant*, *moderate*, and *minimal* hemispatial neglect, respectively. Below each schematic cancellation test are the EEG topographic maps reflecting the degree of hemispheric inactivation at that time. At the far left are the EEG frequency bands: Delta, Theta, Alpha, Beta 1, and Beta 2. At the far right is the amplitude scale for the delta band (25–60 μV) and the other bands (25–40 μV); brighter colors (red and yellow) denote greater amplitudes in any particular frequency band (i.e., reflecting greater hemispheric inactivation). It can be seen that over time (scale at bottom) the degree of left hemispatial neglect decreases in a fashion paralleling the decreasing electrophysiological effects of the amobarbital injection. Number of observations for each condition: *baseline*, $n = 68$; *significant neglect*, $n = 34$; *moderate neglect*, $n = 24$; *minimal neglect*, $n = 36$; and *no neglect*, $n = 47$.


Baseline
Significant Neglect
Moderate Neglect
Minimal Neglect
No Neglect
DELTA
THETA
ALPHA
BETA1
BETA2
Pre-Injection
2 min 3 sec
3 min 50 sec
7 min 2 sec
9 min 59 sec
Delta
All Other Bands
57.667 60.000 39.000 40.000
55.333 57.667 38.000 39.000
53.000 55.333 37.000 38.000
50.667 53.000 36.000 37.000
48.333 50.667 35.000 36.000
46.000 48.333 34.000 35.000
43.667 46.000 33.000 34.000
41.333 43.667 32.000 33.000
39.000 41.333 31.000 32.000
36.667 39.000 30.000 31.000
34.333 36.667 29.000 30.000
32.000 34.333 28.000 29.000
29.667 32.000 27.000 28.000
27.333 29.667 26.000 27.000
25.000 27.333 25.000 26.000

characterized by the patient pointing to the "A"s starting in the far left margin (usually in the upper left corner). Usually, left hemispatial neglect was characterized by the patient beginning in the far upper right corner and then proceeding either leftward and/or downward (to varying degrees, depending on the individual). At some point, they would cease moving leftward, and the test was discontinued. It was this leftward-most movement that was scored for that particular trial for that patient. (Ipsilesional, i.e., right hemispatial, neglect was never observed.) The RLCT was arbitrarily divided into thirds and the patient's neglect was characterized as follows: (1) *significant*: explores the right 1/3 of space, neglecting the left 2/3 of the page; (2) *moderate*: explores the right 2/3 of space, neglecting the left 1/3 of the page; (3) *minimal*: although the patient moves to (or almost to) the left margin of the page, they begin on the right side of the page and move leftward; or (4) *none* (normal): the patient starts at the left margin of the cancellation test and moves rightward. These performance types are depicted in Figure 1, in which the *normal* (and/or no neglect pattern) is shown by the blue arrow, while *significant*, *moderate* and *minimal* degrees of neglect are depicted by the red, yellow, and green arrows, respectively.

EEG Acquisition and Analysis

On the morning of their ISAs, each patient had Ag–AgCl electrodes placed at the following sites: FP1–2, F7–8, F3–4, T3–4, T5–6, C3–4, P3–4, and O1–2. Eye movement electrodes were placed lateral and inferior to one eye. Prior to being submitted to spectral analysis, all recordings were referenced to the ear opposite the injected hemisphere, for example, right hemisphere to left ear. This was done in order to maximize the potential of observing effects in the anesthetized hemisphere by placing the reference as far away as possible.

EEG recording was performed on a BMSI Model 3000 (Biomedical Monitoring Systems, Inc., Los Gatos, CA.) with high- and low-pass filters set at 0.6 Hz (−3 dB down; 18 dB/octave roll-off) and 66 Hz (−3 dB down; 12 dB/octave roll-off). The sampling rate was 200 samples/s with 10-bit resolution. One-minute-long baseline recordings were acquired prior to each ISA. During these periods, eyes were kept open and fixed on a point on the ceiling, while the patient was instructed not to move their eyes and to blink as little as possible.

EEG analysis was subsequently performed offline. The EEG was replayed into a 586/60 microcomputer and analyzed with Rhythm software (Version 10; Stellate Systems, Westmount, Quebec, Canada). The sampling rate was 256 samples/s (with 12-bit resolution), resulting in 2-s sections and a frequency resolution of 0.5 Hz. Online digital filtering was performed with a 15-point finite impulse response filter that attenuates by 50% frequencies at 64 Hz. Acquisition began with the baseline periods and continued until the end of any particular ISA. (The end of the ISA was determined by return of neurobehavioral function, not by EEG normalization.) To ensure stability of the spectral estimates, 2-min periods were analyzed (except for the baselines, which were generally 1 min long). Spectral analysis via fast Fourier transform was performed on these data and spectral densities were calculated for the following bands: Delta (1.5–3.5 Hz), Theta (4.0–7.5 Hz), Alpha (8.0–13.0 Hz), Beta 1 (13.5–20.0 Hz), and Beta 2 (20.5–31.0 Hz).

RESULTS

As described above, each patient's videotape was reviewed and the performance on each presentation of the cancellation test was classified as belonging to one of the aforementioned groups; the time of each performance was also recorded. Forty-two patients were tested twice during their right hemisphere ISA, while 11 were tested once, 15 were tested three times, and 1 was tested four times. Cancellation test performances were grouped according to whether they were *significant* (n obs = 34), *moderate* (n obs = 24), *minimal* (n obs = 36), or *normal*, i.e., *no neglect* (n obs = 47). The EEGs from the particular epoch during which each performance occurred were then averaged.

These data are presented in Figure 2, which shows the degree of neglect graphically at the top, then the corresponding EEG maps for each of the EEG bandwidths, along with the average time at which each level of neglect was seen. Preinjection baseline data are also included (n obs = 68). The scale(s) for the EEG maps were adjusted to show the changes succinctly over time—the black maps during preinjection baseline should not be interpreted as reflecting no EEG activity—rather, the normal baseline EEG (an admixture of Alpha and Beta frequencies at an amplitude of around 20 μV) was present.

Before proceeding, a word is in order about the baseline RLCT map. Although it is colored blue, implying that no area was neglected and the reading pattern was from left-to-right (corresponding to the blue arrow in Figure 1), it should be pointed out that the RLCT was never actually presented prior to the ISA. Rather, we assumed that performance would have been normal based on (1) no prior evidence that any patient manifested hemispatial neglect during extensive neurological and neuropsychological test sessions (including structured letter cancellation tests) and extensive pre-ISA behavioral testing; and (2) in 47/68 (69%) cases, the final cancellation test performance was totally normal, thereby suggesting that a similar performance would have occurred during formal pretesting, had it been carried out. Furthermore, we did not want to prime the patients before the ISA by showing them the cancellation test, thus allowing for the possibility that they might have done better during the ISA by virtue of knowing about how large or extensive the sheet was in reality.

With these caveats about preinjection baseline performance in mind, it can be seen that, over time, the degree of neglect decreases in a monotonic fashion. Similarly, the degree of hemispheric inactivation, as measured by early and profound slowing into the delta and theta ranges, decreases over time, leaving only residual changes in the Alpha, Beta 1, and Beta 2 bands; these changes are in agreement with previous data concerning the time course of EEG changes during the Wada test (Ahern et al., 1994).

- *Significant* neglect tends to occur early on (M = 2 min, 3 s; SD = 1 min, 26 s) during the ISA, with patients neglecting target "A"s in the left 2/3 of the field (red zone). The EEG at this point is characterized by profound slowing into the Delta and Theta ranges, admixed with increases (above baseline) in Alpha, Beta 1, and Beta 2 bands, in zones corresponding to the anterior and middle cerebral artery territories in the inactivated hemisphere. It should be noted that the apparent inactivation of contralateral prefrontal zones is (at least in part) real, although the use of a relatively fixed amplitude scale, along with quadratic interpolation for the maps, tends to exaggerate certain effects, such as contralateral changes appearing more significant than they really are (on the raw EEG tracing).
- Roughly 2 min later (M = 3 min, 50 s; SD = 2 min, 54 s), the degree of neglect has decreased to *moderate*, with patients now neglecting only the left 1/3 of the field (yellow zone). The EEG at this point shows roughly the same admixture of frequencies as the prior observations, although the spatial extent is more restricted.
- Only *minimal* neglect is left by 7 min, 2 s (SD = 4 min, 15 s). In this condition, the patients generally find all of the targets, excepting perhaps those on the extreme left side of the page (green zone). However, they begin by starting on the right (as opposed to the left) side of the page. The EEG now shows significant decreases in the amount of Delta and Theta slow-wave activity. By and large, most activity is centered in the Alpha, Beta 1, and Beta 2 bands.
- By 9 min, 59 s (SD = 3 min, 57 s) postinjection, there is no neglect, with all patients beginning in the far left side of the page and finding all the target "A"s. Curiously, the EEG has not completely returned to baseline at this point, still manifesting increased amounts of fast activity (compared to baseline).

The way the current data were collected meant that not every participant performed the same number of trials, nor did every participant have a performance for each degree of neglect (*significant*, *moderate*, *minimal*, or *none*). As such, the assumptions of a repeated measures analysis of variance would be violated. In an attempt to circumvent this difficulty, multiple regression analysis was utilized to ascertain whether language dominance or side of lesion affected the relationship between the degree of neglect and the EEG changes that occurred in the ISA. Each time the neglect test was presented, there would be an observation including a neglect score (4 for *significant* neglect, 3 for *moderate*, 2 for *minimal*, and 1 for *none*) and the EEG data from each site and band. (For the sake of clarity, only data from right hemisphere sites were used.) These data were submitted to a stepwise multiple regression. Considering the whole data set (n obs = 142), the following EEG variables were selected: T6 Delta, P4 Delta, C4 Theta, and P4 Beta 1. The multiple R was .637, which was highly significant [$F(4,137) = 23.423$, $p < .001$]. To address the language dominance question, separate regressions were calculated for the left language dominant group and those who were not clearly left hemisphere dominant for language (all nonleft-hemisphere language dominant subjects were collapsed because of sample size). The regression (multiple $R = .646$) for the left language group (n obs = 124) selected the identical set of variables to those of the overall analysis. These results were also significant [$F(4,119) = 21.324$, $p < .001$]. In the nonleft-hemisphere language group (n obs = 18), the variables selected were O2 Delta, F4 Delta, and F8 Beta 2. This regression equation (multiple $R = .715$) was not as significant as the other two [$F(3,14) = 4.868$, $p = .016$], but still demonstrated that left hemispatial neglect is dependent on right hemispheric dysfunction. In patients with left hemispheric lesions (n obs = 63), the multiple regression selected T4 Delta, F4 Theta, and C4 Beta 1. The regression equation (multiple $R = .742$) was again highly significant [$F(3,59) = 24.123$, $p < .001$]. Finally, in the right hemisphere lesion group (n obs = 77), a greater number of variables were selected: T6 Delta, P4 Delta, F8 Theta, T4 Theta, C4 Theta, O2 Alpha, FP2 Beta 2, and P4 Beta 2. Once again, the regression equation (multiple $R = .727$) was highly significant [$F(8,68) = 9.545$, $p < .001$].

DISCUSSION

The results of the present study confirm the results of previous studies (Spiers et al., 1990) that demonstrated hemispatial neglect behavior during right hemisphere inactivation in the context of the ISA. This is true regardless of which hemisphere is dominant for language or where the epileptic lesion resides.

In addition, it can now be stated that neglect in the ISA is not an all-or-none phenomenon. Rather, there is a systematic decrease in the extent of hemispatial neglect as the hemisphere recovers its normal function. Even more importantly, the current study demonstrates that these systematic changes in the degree of neglect are paralleled by similar decreases in the amount of hemispheric inactivation, as measured by the spectrally analyzed EEG. While such a resolution of neglect may also occur in right hemisphere strokes, the time course is much longer, which makes such an analysis more difficult.

It is not easy to determine whether the changes in neglect seen in this study are based more on sensory–perceptual *versus* motor–intentional neglect, the former being perhaps more associated with posterior zones in the right hemisphere and the latter being more associated with anterior zones (Bisiach et al., 1990). This is because the letter cancellation test appears to be sensitive to both types of neglect (Daffner et al., 1990). Other methods of measuring neglect, such as extinction to double simultaneous stimulation (tapping sensory–perceptual) and/or blinded motor search for objects on a cork-board (tapping motor–intentional), would have to be used in order to get at this problem. Unfortunately, the time constraints imposed during the ISA make this extensive testing difficult to perform. There is reason to suspect however, that intentional neglect may have been the more important of the two working here. Manoach et al. (1996) failed to find evidence of left hemispatial neglect for mental representations of a familiar scene during the performance of an ISA protocol very similar to the current one. They speculated that the absence of neglect for mental representations might be related to greater inactivation of frontal as compared to parietal–occipital regions during the ISA. Certainly, the current results lend support to that speculation, insofar as the maps presented herein (Figure 2) would seem to show more pervasive and long-lasting inactivation of frontal as compared to parietal–occipital zones. Nevertheless, the multiple regression analyses suggest that EEG activities in multiple zones of the right hemisphere including frontal, temporal, central, parietal, and even occipital in a few instances, correlate with the degree of neglect.

One final interesting observation was even when clinical evidence of left hemispatial neglect had disappeared (i.e., the *no neglect* condition in Figure 2), there were still residual EEG changes (mostly in Alpha and Beta bands) in the right hemisphere topographic maps. This occurred at an average time of 10 min, when, even though lateralized behavioral effects have significantly decreased, some residual changes can still be detected (e.g., mild paraphasic errors during language dominant hemisphere ISAs). This suggests that not only is left hemispatial neglect not an all-or-none phenomenon, but that there is, in addition, a threshold effect, below which, neglect will not be detected (at least by the current means), despite evidence of mild right hemispheric dysfunction (as measured by EEG signs of electrophysiological inactivation).

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