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Failure to Replicate Evoked Potential Observations Suggesting Corpus Callosum Dysfunction in Schizophrenia

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Summary: Somatosensory potentials (SEPs) evoked by vibrotactile finger stimulation have been reported to be the same in both hemispheres in schizophrenics, whereas they are asymmetrical in normals, with the contralateral hemisphere leading the ipsilateral (Jones and Miller, 1981). These findings were taken to indicate that the corpus callosum is nonfunctional in schizophrenics. To attempt replication of these results, vibrotactile SEPs of 6 schizophrenics and 6 normal controls were recorded with both bipolar and monopolar derivations. Assymetrical bipolar SEPs were obtained in both schizophrenics and controls; previous observations of schizophrenic-control differences were not replicated. Acceptable evidence of ipsilateral early SEPs was not obtained; the test procedure seems inappropriate for measuring callosal conduction time.

Jones and Miller (1981) reported results obtained by comparing schizophrenics and nonpatient controls with respect to measurements interpreted as "interhemispheric conduction time across the corpus callosum". Somatosensory evoked potentials (SEPs), elicited by vibratory tactile stimulation of the index fingers, were recorded from scalp locations contralateral and ipsilateral to the stimulated digit. In controls, the poststimulus times of occurrence (latencies) of early peaks were consistently shorter in contralateral than in ipsilateral SEPs; in contrast, the ipsilateral/contralateral latency difficulties were found to be about zero in the schizophrenics. The authors suggested that these findings indicated that "schizophrenia is a split-brain condition akin to agenesis of the corpus callosum".

Connolly (1982) has criticized the Jones and Miller (1981) report on a number of grounds. Connolly notes the differences between the characteristics of the Jones and Miller SEPs and those of Salamy (1978), whose technique they were following; in controls, the amplitudes were much lower, the latencies of the three early peaks shorter, and the ipsilateral/contralateral differences much greater than those reported by Salamy. Connolly takes issue with the idea that the corpus callosum of schizophrenics is nonfunctional, pointing out that, if this were so, it should be easy to demonstrate in these patients the phenomena shown by patients whose corpus callosum has been sectioned; this is certainly not the case. Connolly also points to evidence that only 10 per cent of myelinated callosal axons are of the large diameter type required to conduct the nerve impulses leading to a normal ipsilateral response; furthermore, since about 40 per cent of callosal axons are unmyelinated, the conclusion of Jones and Miller about callosal block would have to be based on a functional test of about 5 per cent of callosal axons.

There are reasons, other than those stated by Connolly (1982), to be concerned about the validity of the results and conclusions of Jones and Miller. Their SEPs were recorded bipolarly, with the vertex lead, (Cz) as a common "reference"; since the vertex lead can be quite active, a spurious "ipsilateral" record can be obtained (Desmedt and Brunko, 1980). Also, the interpretation of ipsilateral/contralateral latency difference as a measure of conduction time across the corpus callosum is at odds with anatomical evidence; while callosal connections have been shown for primary postcentral areas receiving proximal limb projections, they have not been shown for the distal parts of the limbs (Pandya and Vignolo, 1969).

Although there are reasons to question the Jones and Miller findings, they would be very important if valid. Consequently, we attempted to replicate their results. We recorded SEPs to vibratory tactile stimulation with both bipolar and monopolar derivations in schizophrenics and in nonpatient controls. We report

our findings here; they do not replicate those of Jones and Miller.

Method

Subjects

Subjects were 6 schizophrenic patients, ranging in ages from 20 to 37 years (median, 31), of whom 3 were male. The controls were 6 nonpatient paid volunteers, ranging in age from 19 to 36 years (median, 33), of whom 5 were male. The patients met the criteria for schizophrenia of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1980) and also the Feighner *et al* (1972) research diagnostic criteria for definite schizophrenia. One patient had not received psychoactive medication; the others had been receiving fluphenazine (2 cases), haloperidol (2 cases), and chlorpromazine (1 case) for 4 to 22 days before testing. Although the sex composition of the groups was not identical, and most patients were medicated, it will be seen that sex differences and medication could have little bearing on the results.

Recording procedures

A vibrotactile stimulator was constructed by attaching a 1.9 cm diameter wooden button to a 4 ohm speaker voice coil; the button-coil assembly was housed in an enclosure with a hole at the top from which the button protruded, and upon which the subject's finger could rest. The voice coil was driven at a frequency of 400 Hz by a 5 V (peak-to-peak) sine wave provided by an Interstate Electronic Corporation Model F34 generator driving an audio power amplifier. The duration of each stimulus was 50 msec; interstimulus interval was 1.8 sec.

Recording electrodes were chlorided silver cups affixed with EEG paste. Locations were as follows: C3X and C4X, located on the left and right, respectively, 7 cm parasagittal to the midline and 2 cm posterior to the intermeatal plane; Cz, T5, T6, A1 and A2, standard 10-20 system locations (Jasper, 1958); electrooculogram (EOG) monitor over the nasion. Derivations were as follows: C3X-Cz; C4X-Cz; C3X, C4X, Cz, T5, T6 and EOG, each referenced to both ears linked through a 22 Kohm resistor. The 8 derivations were simultaneously recorded under two filtering conditions in 16 channels; in one condition, upper and lower frequency cutoffs, respectively, were 500 Hz and 0.15 Hz, while the values for the other condition were 150 Hz and 1.5 Hz. Averaging (PDP 12 computer) utilized analysis time of 500 msec, sampling interval of 1 msec, and 128 EEG samples per average. A 10 uV biphasic calibration signal was inserted in series with the recording electrodes prior to the stimulus (Fig 1). EEG signals were excluded from the average if the absolute amplitude at T5 or T6 exceeded 10 uV RMS at greater than 50 Hz frequency for at least 50 msec, or if the absolute amplitude at any lead exceeded a voltage equivalent to the dynamic range of the analogue to digital converter. The subject sat in a comfortable armchair with eyes open in a lighted chamber. The stimulator was placed so that the index finger could rest comfortably on the button.

There were four averaging sequences; the second and third, respectively, involved stimulation of the left and right index finger (volar surface of distal phalanx); in the first and fourth, the stimulator was activated in exactly the same way, but the subject did not touch the button. The first and fourth sequences provided controls for the low intensity buzzing sound emitted by the stimulator, which was perceptible even though, during recording, the subject wore earphones transmitting white noise at 75 db SPL.

Amplitude and latency measurements were made by means of a cursor program. Peaks were detected visually and the computer measured amplitude as the deviation from a baseline, determined by taking the mean of the prestimulus data values.

Results

Auditory evoked potentials (AEPs) were recorded to varying degree in different subjects in the nontactile sequences. While clearly seen in the ear reference recordings, the AEPs were markedly diminished or absent in the bipolar tracings; this might be expected, as the voltage gradients from Cz to C3X and C4X were not steep. Since AEPs were of maximum amplitude at Cz, any residual AEP effects in bipolar records would probably be seen in both contralateral and ipsilateral SEPs; the records of S4 (Fig 1) provide an example.

We shall present only the bipolar SEP results in detail. This is because, apart from demonstrating that the vibrotactile stimulator generated clear AEPs, the monopolar recordings contributed little information concerning SEP lateralization that could not be gained from the bipolar tracings. In several subjects (1 of 12 for left index and 5 of 12 for right index stimuli), maximal amplitude contralateral SEPs were at T5 and T6 rather than C3X and C4X, but the latter leads contained essentially the same information. The EOG recordings provided assurance that the scalp lead early SEPs were not of orbital origin.

Fig 1 displays the contralateral and ipsilateral bipolar SEPs to the left and right index finger stimulation of each of the 6 control subjects; to focus on earlier events, only the first 185 msec poststimulus portions of the SEPs recorded with the wider bandpass (500 Hz upper frequency cutoff) are shown. Although

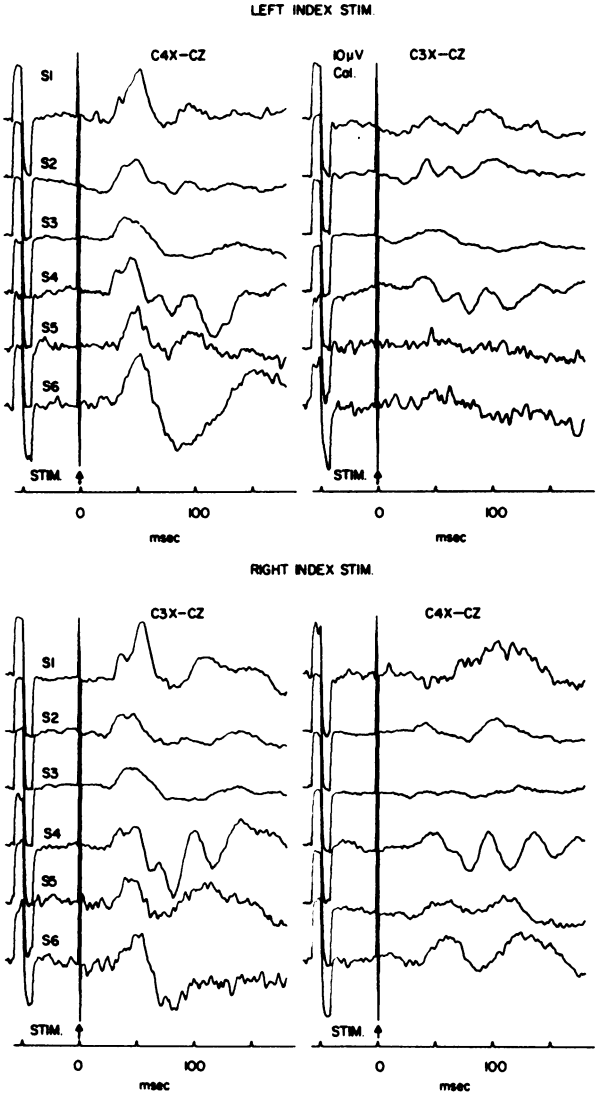

FIG 1.—Bipolar ipsilateral and contralateral SEPs of 6 nonpatient control subjects to left and right index finger tactile stimulation. Relative positivity at C4X and C3X leads give upward deflection. Calibration, 10 uV from maximum positivity to maximum negativity. Note lower amplitude of activity in ipsilateral than in contralateral records

the SEP waveshapes vary considerably between subjects, all of the contralateral records contain a positive peak at about 50 msec. The latencies of this peak ranged from 42 to 54 (mean, 49.5 msec) for the left index and from 43 to 56 msec (mean, 49.3) for right index finger stimulation. Corresponding amplitudes ranged from 1.6 to 4.8 uV (mean, 3.00) for left and from 1.7 to 4.8 uV (mean, 2.46) for right index stimuli. The ipsilateral SEPs either contained no detectable peaks at the same latency (left index, S5, S6; right index, S1, S3) or activity of much lower amplitude. Measurements were made of the maximum amplitude in the ipsilateral SEPs within a window defined by the corresponding contralateral latency ± 5 msec. These ipsilateral amplitudes ranged from 0.0 to 1.7 uV for left (mean, 1.24) and 0.0 to 1.7 uV (mean, 0.55) for right index stimuli; in all cases ipsilateral amplitudes were lower than contralateral. Matched pair "t" tests gave "t" values of 3.98 ($P < .02$) for left and 3.35 ($P < .03$) for right index stimuli. Combining stimuli to both fingers, "t" was 5.38 ($P < .001$).

A positive peak preceding that at 50 msec can be seen in the contralateral C4X-Cz records of S1, S2, and S4 and in the C3X-Cz SEPs of S1, S2, S4 and S6 (Fig 1). The mean latencies and amplitudes of this peak were 36.7 msec and 1.92 uV for C4X-Cz and 37.3 msec and 1.72 uV for C3X-Cz; corresponding ipsilateral maximal amplitudes within the ± 5 msec window defined by the contralateral latencies were 0.53 and 0.35 uV.

Fig 2 displays the bipolar SEPs of the 6 schizophrenic patients. As for the controls, the contralateral SEPs contain early events that are either not visible in the ipsilateral records or of much lower amplitude. The common contralateral peak positivity ranged in latency from 45 to 50 msec (mean, 48.0) in C4X-Cz and 43 to 47 msec (mean, 44.8) in C3X-Cz; corresponding mean amplitudes were 3.54 uV and 2.59 uV. Measurements of the ipsilateral records (maximum at contralateral latency ± 5 msec) gave mean amplitudes of 0.48 uV for C3X-Cz and 0.99 uV for C4X-Cz. Ipsilateral amplitude values were significantly lower than contralateral; matched pair "t" values were 5.72 ($P < .01$) for left index, 6.35 ($P < .01$) for right index and 7.13 ($P < .001$) for left and right combined.

The degree of contralateral/ipsilateral amplitude asymmetry did not differ significantly between patients and controls ("t" <0.6 for all comparisons).

Thus far, the data demonstrate that all of our subjects, both schizophrenic and control, had asymmetrical early SEPs, with larger amplitudes on the contralateral than ipsilateral sides. Because so few subjects had distinct ipsilateral responses, reliable ipsilateral latency measurements could not be made in most cases. Moreover, we had reason to question the nature of the visible ipsilateral activity. The monopolar recordings strongly suggested that, in those cases with an apparent ipsilateral response, it was being contributed primarily by the Cz "reference" lead. This is illustrated in Fig 3 for control S4 (left index stimulus). Each bipolar record represents the difference between the two monopolars, i.e. C4X minus Cz and C3X minus Cz. It will be seen that the early positive peak in

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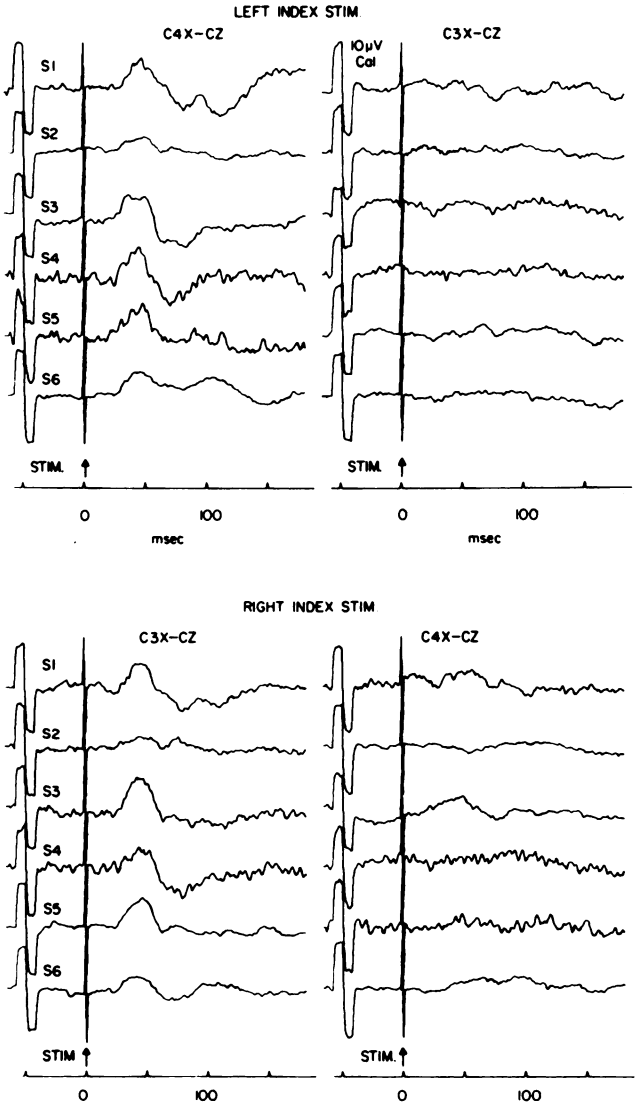

FIG 2.—Bipolar SEPs of 6 schizophrenic patients. Arrangement as in Fig 1.

the C3X-Cz bipolar is contributed primarily from the negativity at Cz, which is greater (more negative) than a corresponding wave at C3X; C3X contains no early positivity in contrast to the two early positive waves, labelled a and b, seen in C4X.

Discussion

Present results showed contralaterally predominant SEPs in both nonpatient controls and schizophrenics. We did not find consistent ipsilateral SEPs at latencies longer than the contralateral SEPs in either group. The degree of contralateral/ipsilateral amplitude asymmetry did not differ between controls and patients. The consistently asymmetrical SEPs would be expected from the projection of the fingers to the contralateral somatosensory cortex, and from evidence that the receiving areas for distal parts of the limbs do not have callosal connections (Pandya and Vignolo, 1969). While failing to replicate the findings of Jones and Miller (1981), our results are in line with anatomical information.

The possibility that medication could have "normalized" the SEPs of our patients seems unlikely. The results of our single unmedicated patient did not differ from those of the other five. Also, Jones and Miller (1981) found no difference between their medicated and unmedicated patients.

We had thought it possible that the use of an active (Cz) reference could have been responsible for Jones and Miller's results, but our monopolar recordings verified the lateral asymmetries seen with bipolar SEPs. It is the case, however, that early positive peak amplitudes in the bipolar records were magnified by the inverted polarity of these peaks at Cz in most instances. Although the bipolar records did not give misleading results with respect to amplitude asymmetry, they could easily suggest the presence of an ipsilateral response not evident in the ipsilateral monopolar recording (Fig 3). Moreover, the latency values measureable from the contralateral bipolar SEPs may not correspond accurately to the early peak latencies in the contralateral monopolar SEPs (Fig 3). We obtained no convincing evidence of early ipsilateral activity in monopolar records; the evident activity could be understood either as volume conducted from the contralateral site or from the vertex lead.

We cannot readily account for the discrepancies between our results and those of Jones and Miller. Two possible problems with their data are suggested by inspection of their Fig 1. First, the normal subject's SEP amplitudes seems sufficiently low to render peak identification, particularly in the ipsilateral SEP, difficult and uncertain; indeed a small positive deflection preceding the ipsilateral peak designated as P1 is about the same amplitude as the contralateral P1. Second, the schizophrenic SEPs contain rhythmic oscillations at a frequency of about 50 Hz; this suggests the possibility that an artefactual signal arising in the 50 Hz electrical mains may have been included in the recording, which would contribute to apparent ipsilateral/contralateral symmetry. Obviously, the problems seen in the two sets of records illustrated

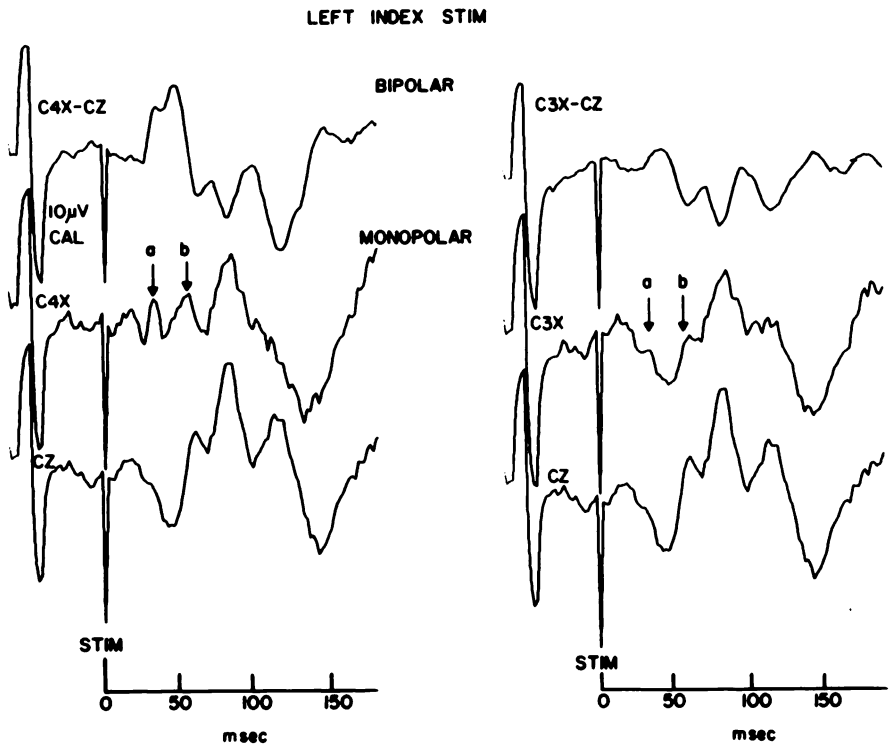

FIG 3.—Illustrates problem of determining at which of two active leads activity in bipolar record originates. Bipolar records same as those for S4 in Fig 1 (left index stimulation). Monopolar records, scalp leads referenced to linked ears, positivity at scalp gives upward deflection. Note two early positive waves, (a, b) at C4X and absence of positivity at the same latencies in C3X record. Apparent positivity in C3X-Cz bipolar record results from greater negativity at Cz than at C3X.

need not necessarily have been present in the remainder of the data.

Our findings have two main implications. (1) Schizophrenics do not obviously differ from normal with respect to SEP hemispheric asymmetry. (2) The procedure involving vibrotactile stimulation of the finger is a questionable approach to the measurement of callosal conduction time. While our negative results cannot be taken as evidence that the corpus callosum functions normally in schizophrenia, they do indicate that the problem should be investigated by other methods.

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