Reversed temporal region asymmetries of P300 topography in left- and right-handed schizophrenic subjects *

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(Accepted for publication: 17 July 1992)

Summary

The auditory P300 evoked potential was recorded in 36 subjects: left-hand (LH) and right-handed (RH) schizophrenic males and LH and RH normal controls. LH and RH normals showed no asymmetry in P300 scalp topography. LH and RH schizophrenics, however, showed lateralized asymmetries in temporal scalp regions: left < right P300 voltage asymmetry in RH schizophrenics and left > right P300 voltage asymmetry in LH schizophrenics. These data suggest that the schizophrenic pathology of P300 neural generators is lateralized according to handedness and provide the first evidence that LH and RH schizophrenics can be dissociated based on left-right voltage asymmetries in P300 topography. These findings further emphasize the need for control of handedness in P300 studies of schizophrenia.

Key words: P300; Schizophrenia; Handedness; Cerebral lateralization

Converging lines of research point to left greater than right hemisphere abnormalities in right-handed (RH) schizophrenic subjects (Crow 1990). Reports of functional and structural left hemisphere abnormalities include: (1) left-lateralized voltage asymmetries in the scalp topography of the auditory P300 (Faux et al. 1990), which are associated with CT evidence of left sylvian fissure enlargement (McCarley et al. 1989); and (2) MRI tissue reductions in the left superior temporal gyrus, which are correlated with auditory hallucinations and thought disorder (Barta et al. 1990; Shenton et al. 1992). Given this and other neuropathological evidence of left hemisphere abnormalities in RH schizophrenics, it has been proposed that schizophrenia is a disease of cerebral dominance (Crow 1986). However, a critical link providing empirical evidence of lateralized pathology in left-handed (LH) schizophrenics has been missing. We here report lateralized asymmetries in P300 topography in temporal scalp regions in LH and RH schizophrenics compared to an overall symmetry in P300 topography in LH and RH normal controls. These data suggest that the pathology of P300 neural generators in schizophrenics is lateralized according to handedness, and that abnormalities, perhaps genetic (Crow 1986, 1990), underlying schizophrenic neuropathology are linked to processes determining cerebral lateralization. These findings further emphasize the importance of controlling for handedness in P300 studies of schizophrenia.

Methods

Eighteen schizophrenic subjects meeting DSM-III-R (APA 1987) and RDC (Spitzer et al. 1978) diagnostic criteria were compared with 18 age- and sex-matched normal control subjects. Subjects, all of whom gave informed consent, were separated into 4 groups based on handedness and diagnosis: 9 schizophrenic RH males, mean age 36 ± 8 years; 9 schizophrenic LH males, 35 ± 10 years; 9 normal RH males, 35 ± 9 years; and 9 normal LH males, 33 ± 8 years. No subject had a history of chemical dependency or neurological illness. Given that degree, as well as direction, of handedness were important considerations for us, we used the Edinburgh Handedness Inventory (Oldfield 1971). This measure, which is based on a set of 20 handedness questions, is designed with a zero point so that scores above or below zero indicate degree or strength of

* This research was supported by an NIMH training grant (DPH); NARSAD (SFF); NIMH Research Scientist Development Award, Scottish Rite Grant (MES); the Medical Research Service of the Department of Veterans Affairs (RWM); NIMH (RWM, AIG); and the Commonwealth of Massachusetts Research Center (DPH, LJS, AIG, RWM).

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right- or left-handedness (Denenberg 1984; Schachter et al. 1987). Scores on the Edinburgh scale range from −100 to +100, with LH or RH preference based on laterality quotients (derived from 100 \times R - L/R + L). Subjects’ scores were +94 ± 9 for RH schizophrenics; −81 ± 15 for LH schizophrenics; +79 ± 18 for RH normals; and −74 ± 9 for LH normals. P300 evoked potentials to the target trials in the attend condition were averaged, and scalp topographic distributions of RH and LH schizophrenics and normal controls were computed from the entire 28-electrode array (international 10–20 system plus interpolated electrodes; see Fig. 1).

Auditory evoked potentials (AEPs) referred to linked ears were recorded during a standard attentive “oddball” paradigm. In the attend condition, subjects were required to count silently the number of infrequent (15%) high-pitched tones (1500 Hz, 97 dB SPL) that were presented within a stream of frequent (85%) low-pitched tones (1000 Hz, 97 dB SPL). Target stimuli were high tones pseudorandomly presented every 1.2 sec (10 msec rise/fall time; 20 msec plateau) against a constant 70 dB white noise background. Subjects were asked to report their counts after every 10–20 target tones (randomly determined). Schizophrenic and normal subjects were able to perform the counting task with mean accuracies of 93% and 98%, respectively, thus ruling out performance deficit as a possible explanation for any mean differences between normal and schizophrenic subjects. AEPs were recorded from a 28-electrode montage which included international 10–20 sites with an additional 8 interpolated sites. Settings for bandpass filters were 0.15–40 Hz. Data sampling was set at 256 data points for each 700 msec epoch.

**Fig. 1.** Topographic distribution of mean integrated P300 voltage during 300–400 msec time window for the 4 groups: (1) LH schizophrenic males; (2) RH schizophrenic males; (3) LH normal males; and (4) RH normal males. Higher positive voltages are color-coded as hotter colors (see scale). RH schizophrenic males show lateral asymmetry with a right-sided shift in P300 maximal voltage compared to the LH schizophrenic males, who show a reversed asymmetry with a left-sided shift in P300 maximal voltage. In contrast, the RH and LH normal males show an overall left-right symmetry in P300 topography. RH normal males show a concentric development of P300 that is maximal in the parietal area; LH normal males show a more anterior development of P300 that is maximal in the centroparietal area.
P300 peak component latency was measured for each attentive waveform and defined as the data point at the Cz electrode with the largest positive voltage within the 200–500 msec time-window. There were no statistically significant differences in latency among the 4 subject groups. P300 integrated voltage was defined as the mean voltage between 300–400 msec, a time-window which best captured the rising phase of the P300 peak (Faux et al. 1990).

Results

Statistical comparisons used the coronal array of electrodes (T3, C3, Cz, C4, T4), which our previous work had shown to reflect P300 asymmetries in RH schizophrenic males. MANOVA analyses showed that overall group effects were statistically significant (Pillai's criterion $F$ equivalent $(5, 28) = 5.16, P < 0.002$). These results indicate that schizophrenic patients had lower overall P300 amplitudes than normals (see Fig. 2), a finding consistent with other studies (Pritchard 1986). Scalp topographic differences among the 4 groups were further statistically analyzed using the profile analysis of parallelism (Morrison 1990) on normalized data (Faux and McCarley 1990) (see Figs. 1 and 2). This analysis showed a significant 3-way interaction of diagnosis $\times$ handedness $\times$ electrode site ($F (4, 29) = 6.54, P < 0.001$; see Fig. 3). To examine scalp topographic differences between selected subject groups, additional multivariate tests were performed. RH and LH schizophrenic subjects showed a significant handedness $\times$ electrode site interaction ($F (4, 13) = 5.51, P < 0.008$), thus statistically supporting the visually striking topographic differences of Figs. 1 and 3. Bonferroni-corrected t tests (2-tailed) on the coronal band of electrodes (T3, C3, Cz, C4, and T4) showed statistically significant differences between the RH schizophrenic and RH normal males at T3 and C3 ($P < 0.05$), and between the LH schizophrenic and LH normal males at C4 and T4 ($P < 0.02$).

Individually, 8/9 (89%) of the RH schizophrenics...
had T3 < T4 voltages while 9/9 (100%) of the LH schizophrenics had the opposite voltage asymmetry, T3 > T4 (P < 0.001, Fisher-Yates test).

Discussion

Since our results show that hand dominance is related to the laterality of P300 voltage deficits in schizophrenia, this study emphasizes the critical importance of controlling for handedness in P300 studies of schizophrenia; it also provides the first evidence that LH and RH male schizophrenics can be dissociated on the basis of left-right voltage asymmetries in P300 topography. These results have implications for theories of functional abnormalities in schizophrenia as related to neuroanatomical structures and cerebral lateralization. At a more direct and experimental level, our findings indicate that it is essential to control for handedness in studies of P300 topography in schizophrenia; mixing LH and RH schizophrenics may cause the distinctive left and right P300 asymmetries to disappear, resulting in a symmetrical P300 topography (Pfefferbaum et al. 1989).

With respect to the broader question of the relationship between hand dominance and brain asymmetry raised by our data, Broca (1861) was the first to note that the left hemisphere is specialized for language, and that handedness may index some aspect of brain organization related to cognitive function. However, despite much research, the exact relationship between handedness and brain asymmetry in humans has remained an intriguing but difficult issue. Empirical evidence based on the WADA test (Rasmussen and Milner 1977), dichotic listening (for recent review, see Kimura 1967, 1983; Annett 1991) and unilateral ECT (Warrington and Pratt 1973) has suggested a strong correlation between right-handedness and the language dominant left-hemisphere, i.e., “standard dominance” in the terminology of Geschwind and Galaburda (1987). In most RH subjects, specialization for language is at least partially localized to the left posterior superior temporal gyrus (STG), an area that includes primary auditory cortex (Heschl’s gyrus) and auditory association cortex (including the planum temporale) (Geschwind and Levitsky 1968; Galaburda et al. 1987). However, while 70% of right-handers are left-lateralized for language and speech (Habib et al. 1990), the relationship among left-handedness and speech and language lateralization is not as clear cut. For example, many left-handers (and some right-handers) are bilateral or right-lateralized for language (Wittelson 1985; Steinmetz et al. 1991), i.e., show “anomalous dominance” in Geschwind and Galaburda’s terminology (1987). Moreover, some studies have reported that, when compared to normals, schizophrenic subjects showed more left-handedness (Katsanis and Iacano 1989; Satz et al. 1990), a functional asymmetry which was associated with an increase in cognitive (Manoach et al. 1986; Katsanis and Iacano 1989) and structural deficits (Katsanis and Iacano 1989; Satz et al. 1990). Our data showed that lateralized P300 deficits were related to hand dominance, suggesting that electrophysiological deficits may be related to “standard dominance” in the RH schizophrenic subjects and to “anomalous dominance” in the LH schizophrenic subjects. Clearly, MRI and post-mortem studies of structural brain asymmetries and anomalies as related to handedness in schizophrenia are needed. Such investigations are currently underway in our laboratories, and our predictions about the structural alterations they will show are discussed below.

ERP studies of schizophrenics have consistently reported a reduced auditory P300 amplitude compared to normals (Pritchard 1986), a deficit which is one of the most replicated biological findings in schizophrenia (Begleiter and Porjesz 1986). Data from stroke lesions provide indirect evidence that this deficit may reflect damage to the temporal lobe generators of P300 (Knight et al. 1989). Initial MRI and EP data from our...
laboratory have provided evidence consistent with bilateral P300 sources, with RH schizophrenics having left-lateralized damage; RH schizophrenics show MRI-defined volume reductions in the grey matter of the left posterior STG (Shenton et al. 1992); these volume reductions are highly and specifically associated with overall P300 amplitude reduction and left < right topographic asymmetry in RH schizophrenics (McCarley et al. 1992). In the present study, the P300 voltage asymmetries in RH schizophrenics were recorded at the same scalp sites shown to be affected by the left posterior STG volume reduction and had a scalp topography consistent with previous studies from this laboratory (see review in Faux et al. 1990). Our data thus lead to the prediction that LH schizophrenics will be found to have right-lateralized STG neuroanatomic volume reductions associated with the left > right P300 voltage asymmetry.

The topographic asymmetry of our LH and RH normal control subjects, which is consistent with previous work on ERPs and handedness in normals (Barrett and Rugg 1989), likely reflects the equal contribution of P300 generators in each temporal lobe. The topographic asymmetry of our LH and RH schizophrenic subjects, in contrast, could reflect some aspect of cellular irregularity in the schizophrenic subjects, irregularities which include cells that are damaged, smaller, fewer in number, distorted, or misaligned. Any of the above histological conditions could contribute to a loss of synchrony or reduction in the number of cells firing and be responsible, at least in part, for the voltage attenuation and lateralized P300 asymmetry in our LH and RH schizophrenic subjects.

Overall, the present study's finding of an opposite P300 asymmetry in LH schizophrenics suggests the possibility of right-lateralized abnormality in this subject group. This finding is consistent with hypotheses which suggest that the pathological process in schizophrenia is one that parallels cerebral specialization, perhaps because of developmental or genetic abnormalities in processes determining cerebral lateralization (Crow 1986). To our knowledge, the present data provide the first evidence consistent with this theory.

References


