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Functional Tests of the Corpus Callosum in Schizophrenia

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Summary: The corpus callosum, a cerebral commissure of 200,000,000 fibres, is thickened in chronic schizophrenia and several neuropsychological and neurophysiological techniques have suggested poor links between the two cerebral hemispheres. The interhemispheric conduction time across the corpus callosum, measured in 12 schizophrenics, using the ipsilateral/contralateral latency differences of the early somatosensory evoked response, was found to be effectively zero. It is suggested that schizophrenia is a split-brain condition akin to agenesis of the corpus callosum, unrecognized through the use of compensatory ipsilateral sensory pathways.

Following the finding at post-mortem of a 20 per cent thickening of the corpus callosum in schizophrenia (Rosenthal and Bigelow, 1972), Beaumont and Dimond (1973) demonstrated that patients had difficulty in matching patterns flashed separately to each visual field, and proposed an analogy between schizophrenia and the split-brain condition found after surgical commissurotomy for intractable epilepsy.

Green (1978) taught schizophrenics to match objects by touch using one hand alone, and found that they had difficulty repeating the task with the other hand. In another study, Green and colleagues (1979) found that schizophrenics comprehended speech better with one ear than with both, suggesting other problems of interhemispheric transfer. This last difficulty could not be demonstrated in bipolar manic-depressives.

Gruzelier and Venables (1974) found that schizophrenics had a less responsive skin conductance on the left than on the right, while Flor-Henry (1976) described large shifting asymmetries in the volage of the electro-encephalogram (EEG) recorded from opposite hemispheres. Both findings could be interpreted as showing a poverty of interhemispheric integration.

Thus, several indirect techniques had suggested that the corpus callosum might not be working as well as it should. When considered with the pathological thickening of the corpus callosum, it seemed likely that the inter-hemispheric conduction time would be prolonged, just as if a peripheral nerve had been damaged and thickened.

The normal inter-hemispheric conduction time had been measured by a technique devised by Salamy (1978). He used vibration given as a stimulus to one index finger, while recording the EEG from both contralateral and ipsilateral sensory areas for the index fingers. The EEG was sampled and averaged by computer over 25 trials immediately after a stimulus, so that the random components of the EEG would be suppressed, while those components occurring at a constant time after the stimulus, presumed to be from sensory neurones firing, would be revealed relatively free of noise. The right side of the body is of course represented in the left cortex, and vice versa.

Vibration is not at all unpleasant compared with the usual median nerve shock, and also gives very distinctive M-shaped waves in the first 100 ms on both sides of the head (labelled P1, N1, P_2 in Fig 1). The topographical distribution of these waves showed a maximum over the sensory cortex, confirming their cortical origin. The response on the ipsilateral side was lower in amplitude and delayed in onset, indicating that it had been relayed across the corpus callosum. Three measures of the conduction time can be calculated by subtracting the contralateral latency from the ipsilateral, using the first positive (P1), first negative (N1), and second positive (P2). The three measures do not give the same value (4, 7, 8 ms in adults), but can be measured independently.

Salamy had validated his technique by showing that the transmission time fell markedly during childhood, in parallel with increasing myelination of the corpus callosum. The ipsilateral response is known to depend on the integrity of the contralateral cortex and corpus callosum as it could be abolished in cats by section of the corpus callosum (Robinson, 1973), and did not develop in humans if the contralateral cortex had been damaged by a cerebral thrombosis (Liberson, 1966).

Method

(a) *Selection of patients*

The twelve schizophrenic patients had been diagnosed as such independently, but one of us (G.J.) interviewed all patients to ensure that they had experienced one or more first rank symptoms of Schneider (1959), in clear consciousness, when not suffering from organic or affective illness. All patients were normal on physical examination, and on routine haematological, biochemical, and radiological tests.

They were consecutive admissions with schizophrenia to two acute wards of a district psychiatric service, with the exception of three patients who refused to be tested, and three patients who were unable to sit still long enough to be tested. Six had been free of neuroleptic medication for at least two months, having previously been on tablets, not long-acting injections, and four of them had never been on neuroleptics. Clinical details are given below.

(b) *Selection of controls*

Controls were hospital staff and students, with no personal nor family history of mental illness, roughly matched with the patients for age and sex (patients 18–67, mean 35.5 years, 8M, 4F; controls 19–63, mean 35.4 years, 9M, 3F). All patients and controls were right-handed.

(c) *Testing methods*

As Salamy's vibrator was complex and expensive, a simple electromagnetic transducer was made to give vibration at an amplitude of 0.5 mm at 400 Hz, in 50 ms bursts at 1.8s intervals. One index finger rested on this.

Electrical activity was recorded from the scalp with Ag/AgCl cup electrodes, fixed with collodion, and an inter-electrode impedance of less than 2 kΩ was achieved with electrode jelly and light scalp abrasion. A reference electrode was placed on the vertex, and active electrodes 6–7 cm lateral to the mid-line and 2–3 cm posterior to the vertex-aural plane, these being approximately over the index finger sensory areas (Duff, 1980). Patients were asked to close their eyes and relax, while lying down in a darkened room.

Recordings were made simultaneously from both contralateral and ipsilateral sides relative to the stimulated finger for 128 trials, then the other hand was used. As the transducer was audible (51 dB), a further test was recorded without mechanical contact to control for possible auditory evoked potentials. The amplified EEG, filtered to 3.2–80 Hz, was sampled and averaged at 512 intervals over 200 ms after the start of each stimulus (Medelec PA63/AA6Mk III/DAV 62).

The distinctive M-shaped waves were identified and their latencies measured by one of us (J.M.) who was blind to the subject's status at the time.

Results

Fig 1 shows the general forms of the evoked responses.

In normals, the ipsilateral response, mediated via the corpus callosum, was smaller in amplitude and delayed in onset compared with the contralateral. Its

TABLE I

Patients	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
Age	18	18	20	22	29	30	34	37	41	52	58	67
Sex	F	M	M	M	M	M	M	M	F	F	M	F
Family history of schizophrenia	+	+	—	+	—	—	—	—	—	+	—	+
Episode	1st	2nd	1st	1st	1st	4th	2nd	2nd	2nd	2nd	1st	1st
Years ill	<1	1	<1	<1	<1	8	4	3	6	8	<1	<1
In/Outpatient	OP	OP	IP	OP	OP	OP	OP	OP	IP	OP	OP	IP
Ill/Remitted	I	R	I	I	R	R	I	I	I	R	R	I
Defect state present	+	+	—	+	—	+	+	+	—	—	—	—
Medicated now	—	+	—	—	+	+	—	—	+	+	—	—
Ever medicated	—	+	—	—	+	+	+	+	+	+	+	—

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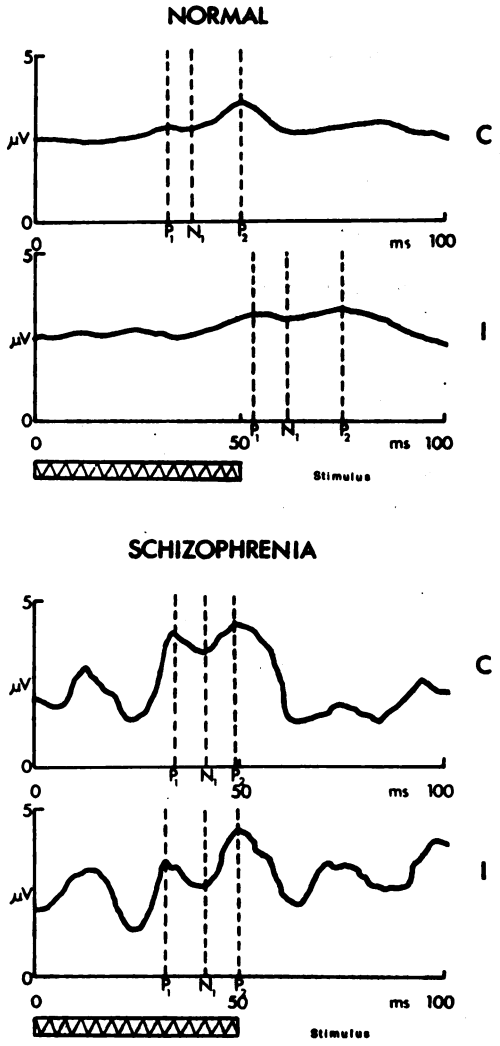

FIG 1.—Contralateral and ipsilateral evoked responses in normals and schizophrenics.
C—contralateral. I—ipsilateral. Positve upwards.
P1, P2—first and second positive waves. N1—first negative.

recording required careful electrode placement as it was so highly localised. The ipsilateral response of schizophrenics showed none of these characteristics, and there was no delayed response as in normals.

Considerable variation in latencies occurred (ranges P1 22–50 ms, N1 30–67 ms, P_2 39–79 ms), especially in the schizophrenic group. However, much of this might have been accounted for by differences in arm length

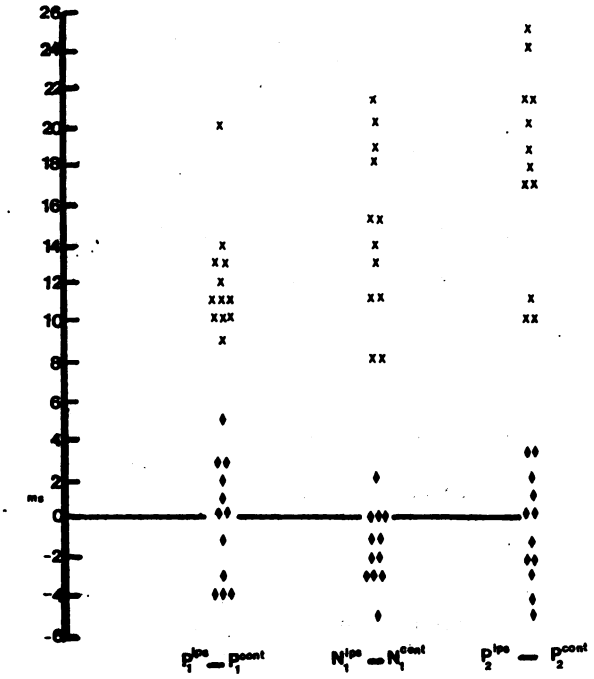

FIG 2.—Latency differences in millisecs between the ipsilateral and contralateral responses (interhemipheric conduction time). × = controls, ◆ schizophrenics.

(heights 148–185 cm). Of more importance is the near synchrony of both ipsilateral and contralateral responses in schizophrenics in the first 100 ms.

Fig 2 shows the latency differences between ipsilateral and contralateral responses in the two groups for the three waves P1, N1 and P2. In schizophrenics, the differences were effectively zero, giving no overlap with normal. This finding is highly unlikely to have occurred by chance.

Discussion

The results in normals are rather longer than those reported by Salamy in 15 adults, probably because of the higher amplitude and frequency of our blunt transducer. It is possible that joint-position receptors were stimulated at this amplitude, so that the transmission times were for a different modality. Gazzaniga and his associates (1975) have demonstrated modality-specific tracts in the corpus callosum, only some being interrupted by partial commissurotomy.

The only previous similar report in schizophrenia was that by Tress and her colleagues (1979) of the synchrony of both 50 ms waves (probably equivalent to our P2) in twelve male patients, all on medication, compared with a 6 ms difference in normals. However,

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TABLE II

Latency differences (ms) between ipsilateral and contralateral responses of the first and second positive (P1, P2) and first negative (N1) waves. Mean ± s.d.

	P1	N1	P2
Controls	12.0±2.9	14.4±4.4	17.7±5.1
Schizophrenics	−0.2±3.1	−1.5±1.9	−0.7±1.3
Mann-Whitney U. test	U = 0 P < 0.001 $n_1=n_2=12$	U = 0 P < 0.001 $n_1=n_2=12$	U = 0 P < 0.001 $n_1=n_2=12$

both stimulus and recording electrode array were different. They found no difference between right and left arm stimulation, which was the case in eight of our patients in whom technically adequate recordings were made from both hands, despite their often restless state.

It is suggested that the ipsilateral response in schizophrenics, almost identical to the contralateral one, is produced by ipsilateral pathways from the brain stem, and that the corpus callosum is not conducting at all. Such an unusual structural rearrangement seems likely as the finding was present whether the patient was on medication or not, and whether in illness or in remission, complete or partial. Ipsilateral pathways are known to exist in animals (Woolsey, 1947), and their enhanced use in humans is one of three possible compensatory mechanisms for a split-brain condition listed by Sperry (1971), who notes their enhancement following birth injuries. The results in the four patients in their first episode of illness, who had never received neuroleptics, suggest that this compensatory mechanism was well developed before their clinical symptoms appeared, and that they had had a corpus callosum that was not conducting for some time.

Therefore, an analogy is proposed between schizophrenia and the pre-schizophrenic state and agenesis of the corpus callosum (Sperry, 1968), a symptomless condition usually discovered accidentally, with only the most subtle of neuropsychological deficits, similar to those found in schizophrenia. Neuropathological examination of the corpus callosum should test this hypothesis.

The thickening of the corpus callosum suggests some damage, and Hare (1980), reviewing the excess of winter schizophrenic births, suggested some perinatal damage, possibly in a winter virus epidemic. Indeed, virus-like agents have been demonstrated in the cerebrospinal fluid of schizophrenics (Tyrrell *et al*, 1979), and might well have persisted for some time. The early onset of corpus callosum problems is also supported by the work of Fish and Hagin (1972), who demonstrated a specific developmental delay at 4–9 months of hand to hand co-ordination in some children at high genetic risk of developing schizophrenia.

Essentially normal results have been obtained in patients with affective disorder, but this is still under systematic investigation. If these are confirmed, then this simple non-invasive technique may help to delineate a clinical syndrome of schizophrenia independently of the known wide variations of diagnostic criteria (Kendell, 1975). The results reported may represent pre-existing subtle structural changes necessary before the functional alterations in the anatomically remote dopaminergic systems usher in the clinical illness (Crow, 1980). Change in the schizophrenic brain at many sites is supported by the finding of enlarged cerebral ventricles in some schizophrenics with long-standing illnesses (Johnstone *et al*, 1978).

If the changes in the corpus callosum do indeed precede schizophrenia, then this technique may prove of value in high-risk research (Garmezy, 1977).

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