cortex (*14*), asymmetries within these pathways could cause lesions of the right hemisphere to affect catecholaminergic neurons differently from identical lesions of the left hemisphere. Although Glick *et al.* found asymmetry in the rat nigrostriatal pathway, the side with greater DA concentration varied among animals. In addition they found no asymmetry in forebrain NE (*6*).

In previous studies we have suggested that post-stroke emotional changes in humans, such as apathy and depression, may be the psychological manifestation of the changes occurring within the catecholaminergic neurons (*1-4*). Our current results suggest that emotional lateralization following brain injury may also be the psychological consequence of the asymmetrical response of catecholaminergic neurons to cortical injury.

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Differences in Neural Organization Between Individuals with Inverted and Noninverted Handwriting Postures

Abstract. *Levy's hypothesis that movements of the distal musculature are controlled by ipsilateral motor projections in subjects with inverted writing posture was tested in a reaction-time experiment with lateralized auditory, tactual, and visual stimulation. Subjects were required to depress a response key with the left or right index finger when they detected a stimulus in either the left or right sensory field. Writers with noninverted posture responded quickest to stimuli on the same side as the responding hand in all modalities tested, whereas inverted writers showed this pattern only in auditory and tactual modalities. In the visual modality, they responded quickest to stimuli on the side opposite the responding hand. Because Levy's hypothesis predicts the latter effect in all modalities for inverted writers, it is challenged by our results, which suggest that inverted writers may be characterized by anomalous visual or visuomotor organization.*

The relation between handedness and cerebral dominance would be relatively simple if there were no left-handers. Whereas more than 95 percent of right-handers are left hemisphere–dominant for language, only 60 to 70 percent of left-handers show this pattern, the remainder being divided into those who have language represented bilaterally and those who have it on the right (*1*). Attempts to predict cerebral dominance in left-handers on the basis of such factors as familial handedness and strength of handedness have not been entirely successful, which indicates that relation among these factors and cerebral dominance in left-handers is not well understood (*1, 2*). It has been proposed, however, that hand posture during writing may provide the best index of cerebral dominance in both left- and right-handers (*3*).

Most individuals assume one of two postures during writing; noninverted, with the hand below the line of writing and the pen pointing to the top of the page; or inverted, with hand above the line of writing and the pen pointing downward giving the hand a hooked appearance. According to a model proposed by Levy (*3*), hemispheric motor projections, such as the pyramidal tracts, that control fine movements of the distal musculature are primarily contralateral in noninverted writers and ipsilateral in inverted writers. Consequently, the language-dominant hemisphere is on the same side as the writing hand in inverted writers and on the opposite side in noninverted writers. The ideas regarding hemispheric motor control, and the predictions that follow from it, are derived, in part, from a genetic model of handedness and cerebral dominance (*4*). It states that cerebral dominance is determined by one gene and handedness is determined indirectly by a second gene that specifies whether the dominant hand will be ipsilateral or contralateral to the language-dominant hemisphere.

Levy and Reid (*5*) found that the pattern of hemispheric specialization as reflected in the performance of normal people on tachistoscopic laterality tests was in accordance with the model. In identifying unilaterally presented nonsense syllables, noninverted writers favored the visual field on the same side as the writing hand, thereby implicating the hemisphere contralateral to it as the dominant one for language. Inverted writers showed the opposite pattern of results, except for diminished perceptual (and presumably hemispheric) asymmetries, which suggests that in this population speech is relatively bilaterally represented (*1*).

Not all attempts to verify this hypothesis were as successful. A number of investigators (*6-8*) using a variety of techniques, including tachistoscopic ones, to assess cerebral dominance either found no relation between hand posture and speech lateralization or a weak correlation. Rather than attempt to assess language lateralization yet another time, we decided to test that aspect of the model that deals with hemispheric control of the distal musculature. This problem is central both to the model on hand posture during writing and cerebral organization and to the genetic model (*4*) of handedness and cerebral dominance. In addition, there was no direct empirical evidence on the validity of the assertion that fine motor movements are controlled by the ipsilateral hemisphere in inverted writers or, for that matter, in anyone. This notion is so contrary to widely held views of structural and functional neuroanatomy (*9*) that any evidence in its favor would have far-reaching implications on our ideas of the organization of the nervous system. Negative evidence, on the other hand,

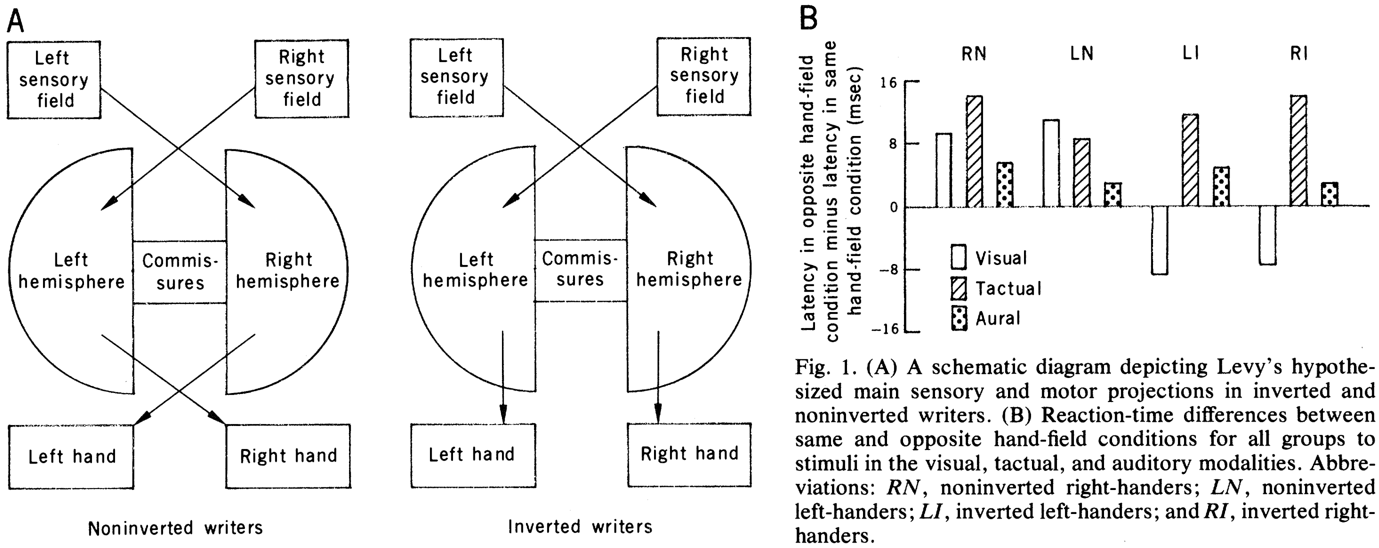

Fig. 1. (A) A schematic diagram depicting Levy's hypothesized main sensory and motor projections in inverted and noninverted writers. (B) Reaction-time differences between same and opposite hand-field conditions for all groups to stimuli in the visual, tactual, and auditory modalities. Abbreviations: *RN*, noninverted right-handers; *LN*, noninverted left-handers; *LI*, inverted left-handers; and *RI*, inverted right-handers.

would seriously challenge the above models. Rather than finding differences in the motor system, our experiments show fundamental differences between inverted and noninverted writers in the organization of the visual or the visuomotor system.

To test the hypothesis on hemispheric motor control, we chose a simple reaction-time procedure in which individuals were asked to respond as quickly as possible, with either the right or left hand, to a stimulus that appeared in either the right or left sensory field. The visual, auditory, and tactual modalities were tested separately for each individual. To avoid engaging the specialized processing mechanisms of either hemisphere, the stimuli were simple, unpatterned, and salient (*10*): a dot, a pure tone, and a touch. The strongest sensory pathways in each of these modalities project primarily to the contralateral hemisphere (Fig. 1A). Response times in any of these modalities will be shortest to a stimulus that has the most direct access to the hemisphere emitting or controlling the response. According to conventional neuroanatomical notions, latencies would favor stimuli that appeared in the sensory field on the same side as the responding hand (same hand-field condition) regardless of the individual's handedness or writing posture. If the model is correct, however, this would be true of only noninverted writers (see Fig. 1A). Inverted writers, whose responses are controlled by uncrossed motor pathways, would respond more quickly to a stimulus in the sensory field opposite the responding hand (Fig. 1A). Only performance in the visual modality supported the prediction from the model.

One faculty member, one fourth-year graduate student, and 35 undergraduates were divided into four groups on the basis of writing hand and writing posture (*11*). There were six males and six females in each of the following three groups: right noninverted, left noninverted, and left inverted. Because right inverters are rare, the final group consisted of one undergraduate female. All subjects reported normal hearing and normal or corrected-to-normal vision.

The experiment was conducted in an illuminated room with an ambient noise level of about 50 dB. The subject sat at a table and rested the index finger of either the left or right hand on a response key. A warning signal was followed about 1 second later by a stimulus trial or a blank trial which ensured that the subject did not anticipate the stimulus. The subject was required to depress the key as quickly as possible when the stimulus was detected and to refrain from responding during blank trials (*12*). The test stimulus was presented randomly, but equally often, to either the left or right sensory field for 150 msec. The onset of a stimulus triggered a millisecond timer that was stopped by the subject's response. The reaction time was recorded by the experimenter who sat opposite the subject.

Each modality was tested separately. There were 400 trials each in the visual and tactual modalities and 416 trials in the auditory modality, divided equally into two sessions. Half were stimulus and half were blank trials. In one session the subject responded with the left hand; in the other, with the right. The orders of responding hand and of test modality presentation were counterbalanced across subjects (*13*).

Tactile stimulation was accomplished by releasing a 4.395-g Guardian Electric (#4X7) tapered solenoid pin onto the center of the middle fingernail from a distance of 2 mm (*14*). Each middle finger was positioned beneath one solenoid and the solenoid-to-finger distance was adjusted. A microswitch-response key was then mounted beneath the index finger. Subjects were instructed to close their eyes and prepare to respond when the experimenter tapped the desk. If it was a stimulus trial, the experimenter released either the left or right solenoid about 1 second later. The intertrial interval was about 5 seconds, during which latencies were recorded.

In the visual condition, subjects were shown 6 by 4 inch index cards in a rear-loading Cambridge two-channel tachistoscope (BRD Electronics) and were required to respond when a laterally positioned 3-mm dot appeared 2° of visual angle to either the left or right of a centrally located 2-mm fixation point. Luminances were 21.47 and 17.86 mL for preexposure and stimulus fields, respectively. Subjects were instructed to focus on the fixation point when the experimenter tapped the desk and to prepare to respond. About 1 second later a stimulus or blank trial was presented. The intertrial interval was 5 to 7 seconds, during which the experimenter recorded the reaction time and changed stimuli (*15*).

Auditory stimuli were pure tones presented against a white noise background with a signal-to-noise ratio of 24 dB. A 300-msec, 350-Hz binaural tone that served as a warning signal was followed 1 second later by a 150-msec, 1000-Hz monaural test tone in the left or right channel on half of the trials, and by nothing on the other half. The stimuli were taped and played on a Revox A-77 tape recorder and delivered through TDH-39 stereo earphones (*16*). Onset of the monaural test stimulus activated an ERC digital millisecond timer (Textron Ltd.)

through Schmitt triggers. Unlike testing in other modalities, trials were arranged randomly in four blocks of 52 trials with a 6-second intertrial interval. Subjects were tested with their eyes closed.

Table 1 presents mean group reaction times for each modality according to responding hand and side of stimulation (*17*). Differences between inverted and noninverted writers were found only in the visual modality. As expected, noninverted writers responded quickest to stimuli in the sensory field on the same side as the responding hand in all the modalities tested. Inverted writers, however, followed this trend only in the auditory and tactual modalities. In the visual modality, inverted writers responded quickest to stimuli in the visual field opposite the responding hand (Fig. 1B). There were no significant group effects or interactions in the tactual and auditory modalities (*18*) [$F(2, 33) = 0.75$, $P = .45$; and $F(2, 33) = 1.76$, $P = .18$, respectively], which indicates that all groups behaved similarly. Not one subject showed the pattern predicted by the motor control hypothesis in both of these modalities. However, there was a highly significant group-responding hand-field interaction in the visual modality [$F(2, 33) = 21.58$, $P < .001$]. As expected, the responding hand-field interaction was highly significant in all three modalities: auditory, $F(1, 33) = 20.35$, $P < .001$; tactual, $F(1, 33) = 103.33$, $P < .001$; and visual $F(1, 33) = 5.86$, $P < .02$. This indicates that latencies were fastest to stimuli having direct access to the hemisphere controlling the responding hand (*19, 20*).

If the hypothesis on hemispheric motor control were correct, inverted and noninverted writers would show opposite sensory field advantages in each modality in our reaction-time tasks (Fig. 1A). That such differences were found only in the visual modality seriously challenges this hypothesis as well as the models (*3, 4*) that depend on its validity. Our failure to find evidence of ipsilateral motor control is consistent with the observations that unilateral hemispheric anesthetization rarely, if ever, produces a hemiplegia that is primarily ipsilateral to the affected hemisphere (*7*) and that electrophysiological activity is greatest over the parietal region contralateral to the moving hand, even in inverted writers (*6–8, 21*).

Table 1. Mean reaction times and standard deviations in response to simple visual, tactual, and auditory stimuli according to responding hand and side of stimulation. The numbers in parentheses indicate the number of subjects in each group performing in accordance with the group average. Groups: left noninverted (LN), left inverted (LI), right noninverted (RN), and right inverted (RI).

Group	Responding hand					
	Left			Right		
	Side of stimulation			Side of stimulation		
	L (msec)		R (msec)	L (msec)		R (msec)
Visual						
RN	266.8 ± 47.9	(9/12)	273.5 ± 51.7	274.7 ± 46.0	(11/12)	262.9 ± 43.8
LN	277.5 ± 45.2	(9/12)	285.4 ± 52.2	276.1 ± 47.7	(9/12)	262.7 ± 46.7
LI	275.7 ± 44.9	(9/12)	265.1 ± 45.7	259.3 ± 41.2	(9/12)	266.1 ± 42.8
RI	234.5 ± 27.5	(1/1)	229.9 ± 28.5	240.2 ± 59.9	(1/1)	250.1 ± 48.1
Tactual						
RN	221.9 ± 33.0	(11/12)	233.3 ± 42.0	247.5 ± 43.6	(11/12)	231.1 ± 34.9
LN	221.9 ± 40.0	(8/12)	226.2 ± 37.3	217.7 ± 42.8	(11/12)	205.0 ± 36.2
LI	213.1 ± 37.4	(9/12)	221.2 ± 36.5	236.1 ± 44.0	(10/12)	221.7 ± 36.7
RI	168.8 ± 14.0	(1/1)	186.7 ± 17.8	185.2 ± 37.9	(1/1)	175.9 ± 23.8
Auditory						
RN	189.0 ± 35.8	(9/12)	192.4 ± 35.8	193.6 ± 43.7	(9/12)	187.0 ± 38.1
LN	188.4 ± 35.4	(9/12)	190.9 ± 34.4	181.0 ± 38.2	(6/12)	178.3 ± 30.5
LI	180.4 ± 30.0	(8/12)	181.2 ± 33.6	183.6 ± 30.7	(9/12)	176.1 ± 28.6
RI	178.5 ± 31.8	(1/1)	179.4 ± 25.2	166.4 ± 19.9	(1/1)	162.1 ± 17.5

Our results, instead, suggest that the differences in neural organization between inverted and noninverted left-handers lie primarily in the visual system or its interface with the motor system. Inverted writing postures can be viewed as a form of compensation for an abnormal visual, or visuomotor, organization. In these studies we noted that inverting the hand makes it easier for individuals with a noninverted writing style to write English upside down so that the text reads from right to left (*22*). Perhaps inverted writers adopt that posture regularly because of some anomaly in their visual or visuomotor representation of the world. In cultures where the direction of writing is opposite to English, from right to left, such compensation may not be necessary. The incidence of inversion in writers of Hebrew is less than 10 percent even in left-handers, compared to about 50 percent in American left-handers (*23*).

Our visuomotor hypothesis is compatible with the finding of Herron *et al.* that electrophysiological differences between inverted and noninverted writers occur only at occipital leads (*8*). It is also consistent with the finding that those laterality tests with a strong component best distinguish inverted from noninverted left-handers (*6*).

The exact nature of the neural anomalies in inverted left-handers, however, is still uncertain (*24*). For the present we are satisfied to have demonstrated that there are definite differences in neural organization between inverted and noninverted writers, and that they seem to involve the visual or visuomotor system.

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11. The latter classification was determined by requiring each subject to write a sentence on lined paper that was aligned vertically with the edge of the table. If the pen pointed toward the subject and the hand was held above the line of writing, the subject was classified as an inverter. If the pen pointed away and the hand was held below the line of writing, the subject was classified as a noninverter.
12. This was, a simple reaction-time procedure in which the subject responded whenever a stimulus was present and withheld a response on catch trials. Because stimulus discrimination was not involved, the procedure was considered a Donders type a.
13. Each session was divided into four blocks of an equal number of trials. Equal numbers of stimulus and blank trials were in each block and they varied randomly with each other. The order of presentation followed a predetermined random sequence. Experimental trials were preceded by 25 practice trials. Short breaks were permitted between blocks or whenever the subject complained of fatigue or boredom. Ideally the experiment required two 1.5-hour sessions per subject with two modalities tested per session, but deviations occurred because of scheduling problems.
14. Two solenoids were attached by sliding collars to two vertical posts mounted on separate 12.7 by 12.7 cm Plexiglas bases. A Grason-Stadler power supply (Model E1100DA) was used, and the onset and duration of solenoid presentation was controlled by a Gerbrands series 300 integrated-circuit millisecond timer.
15. To provide a relatively fixed interval between warning signal and trial in the visual and tactual conditions, a centrally placed Birkbeck timer and signal source repeated 50-msec bursts of noise at 1-second intervals. The experimenter gave the warning signal simultaneously with one burst and presented the stimulus on the succeeding burst. The subject was made aware of this procedure.
16. The sinusoidal tones were computer-generated and aligned and played at an intensity of 86 dB (sound level) measured by a General Radio 1565-A sound level meter through a 1560-P82 earphone coupler.
17. The means and standard deviations were calculated for each session for each subject. Because we wished to discard those trials on which the subject was either inattentive or anticipated stimulus presentation, we excluded all trials in which the reaction times were 2 standard deviations different from the mean. The mean was then recalculated. Typically, about 1.5 trials in 50 were excluded. This procedure affected the outcome, in terms of which sensory field was favored for a given response hand, in only one subject. Also, if standard deviations were very high (more than 100 msec) or more than ten errors were committed during one session, we assumed that the subject was inattentive and the session was rerun. This was necessary for only four of the 222 sessions.
18. Separate analyses of variance were made for each modality, with group as the between-subject variable and responding hand and sensory field as the within-subject variables. The single inverted right-hander could not be included in the analysis.
19. Neither responding hand nor field of stimulation appears to have clearly influenced reaction times, except in the tactual modality where reaction times tend to be shorter for right field stimulation [$F(1, 33) = 6.49, P = .16$]. The latter finding is irrelevant with regard to the hypotheses under consideration.
20. The latency differences between sensory fields were small and close to electrophysiological measures of interhemispheric transmission times [F. Bremer, *Res. Publ. Assoc. Res. Nerv. Ment. Dis.* **36**, 424 (1958); B. Grafstein, *J. Neurophysiol.* **22**, 504 (1959); L. T. Rutledge and T. T. Kennedy, *Exp. Neurol.* **4**, 470 (1961); H. Teitelbaum, S. W. Sharpless, R. Byck, *J. Comp. Physiol. Psychol.* **66**, 623 (1968); A. Salamy, *Science* **200**, 1409 (1978) and references therein; A. Ledlow, J. M. Swanson, M. Kinsbourne, *J. Exp. Psychol. Hum. Percept Perform.*, in press]. Consequently they are likely to reflect neuroanatomical relations rather than differences in spatial compatiblity between stimulus and response where latency differences, as well as overall response times, are much longer [D. E. Broadbent and M. Gregory, *J. Exp. Psychol.* **63**, 575 (1962); R. J. Wallace, *ibid.* **88**, 354 (1971); J. Callan, D. Klisz, O. A. Parsons, *ibid.* **102**, 1039 (1974)]. Lastly, the simple reaction-time procedure we employed corresponds to a Donders type a which is not prone to significant spatial compatibility effects [G. P. Anzola, G. Bertolini, H. A. Buchtel, G. Rizzolatti, *Neuropsychologia* **15**, 295 (1977); G. Berlucchi, F. Crea, M. DiStefano, G. Tassinari, *J. Exp. Psychol. Hum. Percept. Perform.* **3**, 505 (1977)].
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24. One possibility is that the visual projections are uncrossed. Although such anomalies have been found in albinos [D. Creel, F. E. O'Donnell, Jr., C. J. Witkop, Jr., *Science* **201**, 931 (1978)], preliminary electrophysiological evidence makes this possibility very unlikely in our population. A more likely alternative is that the anomaly lies at the interface of the visual and motor systems. In this connection, W. Richards' study [*Exp. Brain Res.* **17**, 333 (1973)] on subcortically mediated stereoscopic depth perception in individuals with scotomata of occipital origin may be instructive. In one individual, the identical stimulus lateralized to a scotomatous half-field changed from being reported in front to in back of the plane of fixation only when he responded with the hand opposite the stimulated field. This suggested to Richards that there may be contralateral inhibitory somatosensory-visual connections in the tectum that influence perception in the contralateral field. One has simply to assume ipsilateral influences in inverted left-handers to account for the results of our experiments as well as the observation that inverted writing occurs most in cultures where the direction of writing is from left to right. However, this hypothesis is speculative and requires much more research to substantiate.
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Delayed Neurotoxicity of Phenylphosphonothioate Esters

Abstract. *Administration of a single oral dose of five phenylphosphonothioate esters produced delayed neurotoxicity in hens; their potency was, in descending order, cyanofenphos, EPN, desbromoleptophos, leptophos, and EPBP (Seven). Histological examination showed that in some hens there was marked axonal and myelin degeneration in the spinal cord and peripheral nerves. The results suggest that delayed neurotoxicity may be a general feature of phenylphosphonothioate insecticides.*

Although organophosphorus pesticide–induced delayed neurotoxicity may be produced by some organophosphorus esters, most of these compounds cause acute poisoning with temporary muscle weakness (*1*). The delayed neurotoxic effect was first demonstrated in humans (*2*); later, some additional species were found to be susceptible (cats, dogs, cows, and chickens), while others were not (rodents and some primates) (*3*). The test animal chosen to demonstrate this syndrome is the adult chicken. The clinical condition is recognized as ataxia, which develops 4 days or more after administration. Lesions are characterized by degeneration of axons with subsequent Wallerian degeneration of myelin. Recently, the phenylphosphonothioate insecticide leptophos has been implicated in the poisoning and paralysis of some workers in Texas (*4*). Leptophos produces delayed neurotoxicity in farm animals and chickens (*5–9*). A photodegradation product of this compound, desbromoleptophos (DBL), was reported to cause delayed neurotoxicity in chickens (*10*). Another insecticide in this group, EPN, caused delayed neurotoxicity when fed (*11*) or orally administered (*12, 13*) to chickens. I report here the ability of two other phenylphosphonothioate insecticides, EPBP and cyanofenphos, to cause delayed neurotoxicity in hens. I also report the relative neurotoxic potencies of the five phenylphosphonothioate esters: leptophos, DBL, EPBP (*S*-Seven), EPN, and cyanofenphos (Fig. 1).

Experiments were performed with adult hens (*Gallus gallus* domesticus), mixed breed (Spafas, Inc., Norwich, Connecticut), each 1 year old and weighing approximately 1.5 kg. Eight groups of hens (three each) were given a single oral dose of each compound in a gelatin capsule; dose ranges (in milligrams per kilogram of body weight) were: leptophos, 10 to 3000; DBL, 10 to 100; EPBP, 100 to 5000; EPN, 10 to 500; and cyanofenphos, 5 to 250. Hens given all doses of EPN and high doses of the other insecticides had been previously treated with a single oral dose of atropine sulfate (30 mg/kg) in water as protection against the acute toxicity of these esters. Controls consisted of four groups of hens orally given empty gelatin capsules, tri-*o*-cresyl phosphate (TOCP) (500 mg/kg), parathion (10 mg/kg) with atropine sulfate (30 mg/kg), or atropine sulfate (300 mg/kg). The birds were supplied with food and water ad libitum. Body weights were monitored and hens were examined periodically for neurological signs of delayed neurotoxicity. Nerve tissues were