

Asymmetrical hand force persistence and neuroleptic treatment in schizophrenia

SCOT E. PURDON, NEIL D. WOODWARD, AND PIERRE FLOR-HENRY

The University of Alberta and The Alberta Hospital Edmonton, Edmonton, Alberta, Canada

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Abstract

The recent development of an isometric instrument for the precise quantification of hand force persistence has created a novel opportunity for the evaluation of potential motor asymmetries in schizophrenia and their response to treatment. A study of asymmetries in the unmedicated state may provide insight into the pathogenesis of schizophrenia, whereas alterations of asymmetries in response to antipsychotic medication could assist the delineation of a cerebral mechanism for the effects of pharmacotherapy. The hand force persistence of 21 unmedicated patients with schizophrenia was compared to 21 age, gender, and handedness matched normal controls. The effect of neuroleptic treatment on hand force persistence was then evaluated on a subset of 10 patients after at least 30 days of treatment. The anticipated asymmetry was evident in the unmedicated sample that showed impaired right hand force persistence compared to the normal control sample. The prospective comparison showed an alleviation of the asymmetry resulting from an improvement of right hand force persistence with treatment. In addition to providing further support to a primary left hemisphere cerebral involvement in schizophrenia, the present results suggest that prior investigations of motor asymmetry may have been compromised by the study of medicated patients. The apparently paradoxical improvement of motor skill may relate to the substantial number of patients treated with 2nd generation neuroleptic medications which may implicate an improvement in left hemisphere physiology in the cognitive advantages of the novel treatments. (*JINS*, 2001, 7, 606–614.)

Keywords: Schizophrenia, Neuropsychology, Motor, Asymmetry, Neuroleptic

INTRODUCTION

A resurgence of interest in a neurodevelopmental basis for schizophrenia has contributed to renewed interest in the pathophysiological role of the left cerebral hemisphere described 30 years ago (Flor-Henry, 1969; Flor-Henry & Gruzelier, 1983; Gur & Chin, 1999). The development of novel pharmacotherapeutic agents with the potential to reduce the cognitive impairment in schizophrenia has also raised interest in alterations of cerebral laterality with treatment (Purdon, 1999, 2000). The occasional skepticism expressed about the validity of a prominent left hemisphere involvement may relate to inconsistent observations from *in vivo* structural neuroimaging often but not invariably implicating a left cerebral pathology (e.g. Buckley, 1998; Weinberger & Lipska, 1995). The structural results contrast with physio-

logical investigations of sensorimotor cortex activation under motor challenge which have more consistently revealed left hemisphere dysfunction in unmedicated samples on positron emission tomography (PET) and regional cerebral blood flow (rCBF) (Buchsbaum et al., 1992; Guenther et al., 1986b). Similar investigations with medicated patients have also observed left hemisphere dysfunction on PET, functional magnetic resonance imaging (fMRI), and electroencephalography (EEG) (Guenther et al., 1985, 1986a, 1994; Schroder et al., 1995), although there are also idiosyncratic reports of bilateral physiological dysfunction in medicated samples (Mattay et al., 1997; Schroder et al., 1999).

The discrepancy between structural and functional neuroimaging may implicate a more robust physiological relative to structural cerebral asymmetry associated with schizophrenia that may have a behavioral manifestation in asymmetrical cerebral dysfunction in motor and sensory systems. A recent review of the literature pertaining to sensory asymmetries suggested the accuracy of this prediction despite ambiguous results of prior studies of medicated patients

Reprint requests to: Scot E. Purdon, Neuropsychology-9 Bldg., Alberta Hospital Edmonton, Box 307, 17480 Fort Road, Edmonton, T5J 2J7, Ab Canada. E-mail: scot.purdon@amhb.ab.ca

with schizophrenia (Purdon & Flor-Henry, in press). For example, unmedicated patients demonstrate a reliable right sided impairment of the contralateral perceptual systems for auditory, visual, and haptic stimuli, as well as a left nostril acuity deficit in the predominantly ipsilateral olfactory system, all of which show a reduction of the asymmetrical deficit with neuroleptic treatment (Purdon & Flor-Henry, in press; Seidman et al. 1993; Tomer, 1989; Tomer & Flor-Henry, 1989). A similar mitigation of cerebral asymmetry with antipsychotic medication was suggested for the motor system in a prospective study of schizophrenia showing a shift in the Hoffman reflex recovery curve from a relative right to a relative left side advantage following neuroleptic treatment (Tan & Gurgen, 1986). Also, unmedicated patients have a left rotational preference (Bracha, 1987), a slowing of right hand finger tapping speed (Gorynia & Uebelback, 1992), and a relative excess of right hand tremor (Caligiuri & Lohr, 1993), whereas medicated patients have bilateral impairments of finger tapping speed (Ragland et al. 1999), finger-thumb opposition (Walker & Green, 1982), and hand force persistence (Caligiuri & Lohr, 1990). Additional studies of hand force persistence in both medicated and neuroleptic naïve patients have implied a right hand deficit based on observed asymmetries in schizophrenia relative to normal samples, however, the right hand comparison between groups was not reported (Lohr & Caligiuri, 1995, 1997). There is thus sufficient evidence to suggest abnormal motor asymmetries in schizophrenia that may show alteration with antipsychotic treatment.

The hand force persistence task provides a measure of fine motor control that may be particularly sensitive to cerebral asymmetry and medication effects (Caligiuri & Lohr, 1993; Caligiuri et al., 1993). An experiment was devised to test the anticipated motor asymmetry by measurement of hand force persistence in normal controls and a sample of patients withdrawn from neuroleptic treatment for a minimum of 7 days. We hoped to replicate the hand force asymmetry in schizophrenia relative to the control group and further demonstrate that unmedicated patients would show a significant deficit of the right hand compared to the control sample. The hand force examination was repeated in a subgroup of patients who were suitable for treatment and follow up within the Alberta Hospital Edmonton (AHE) Neuropsychology Service after at least 4 weeks of antipsychotic medication. We anticipated a medication-based mitigation of the motor asymmetry to result from a significant improvement of right hand force persistence.

METHODS

Research Participants

Twenty-one unmedicated patients with schizophrenia or schizoaffective disorder were matched to 21 normal controls by age, gender (17 male and 4 female per group), and hand dominance (12 strong right, 8 inconsistent right, and 1

mixed right per group). Patients were recruited from the inpatient service and controls were recruited from staff at AHE. Age of onset ($M = 26.99$ years, $SD = 9.09$) and duration of illness ($M = 2.73$ years, $SD = 3.07$) defined a relatively early phase sample of undifferentiated ($n = 10$), disorganized ($n = 2$), paranoid ($n = 6$), residual ($n = 1$), and schizoaffective ($n = 2$) patients. Psychopathology rating scales (PANSS) administered to the patient sample indicated a mild positive syndrome ($M = 21.76$, $SD = 8.50$), a moderate negative syndrome ($M = 26.86$, $SD = 4.95$), and a mild global syndrome ($M = 44.29$, $SD = 10.43$) of psychopathology. Also, examination of extrapyramidal motor symptoms (ESRS) revealed the presence of dyskinesia (very mild: $n = 4$; mild: $n = 1$) and parkinsonism (very mild: $n = 3$; mild: $n = 1$; moderate: $n = 2$) but not dystonia in the patient sample. Only one patient screened for inclusion exhibited sufficient movement disorder to meet Schooler and Kane's (1982) research diagnostic criteria for tardive dyskinesia and this patient was not included in the sample of 21 patients reported here. Medication history and chart review documented neuroleptic naïve status in 7 patients. Among the remaining 14 unmedicated patients, washout periods for all medications were 7 to 14 days ($n = 8$), 15 to 21 days ($n = 3$) and 22 to 28 days ($n = 3$). The medication withdrawal period was determined by multiplication by 5 of the daily half-life of the last-received neuroleptic treatment as reported in the 1999 Compendium of Pharmaceuticals and Specialties (CPS, 1999). Of the 14 previously medicated patients, 4 had last received a typical and 10 had last received an atypical neuroleptic prior to washout. Consistent with the age-matching rule of ± 4 years, the patient group ($M = 29.76$, $SD = 9.68$) was similar to the control group ($M = 29.43$, $SD = 8.63$). Average educational level of the patient sample was approximately Grade 12 ($M = 12.38$, $SD = 2.56$), significantly lower than the third-year college level of the control sample [$M = 15.62$, $SD = 3.09$], $t(42) = 3.70$, $p < .001$]. Estimated general intellect (PPVT-R) was in the low average range for the patient sample ($M = 95.05$, $SD = 20.29$), also significantly lower than the high average level of the control sample [$M = 111.67$, $SD = 12.54$; $t(42) = 3.19$, $p = .003$]. All participants reported normal motor ability and were free from any prior neuromuscular or skeletal disorder, electro-convulsive therapy, head injury with significant loss of consciousness (i.e., >29 min), or recreational inhalation of glue or gas.

Of the original sample of 21 patients, 10 consented to be reexamined following 30 days of neuroleptic treatment. The remaining 11 patients either refused to be reexamined, failed to adhere to their prescribed treatment plan, or were discharged from the hospital and lost to follow-up. The subset was in all respects similar to the general sample, and consisted of 7 strong right, 2 inconsistent right, and 1 mixed right handed males according to Annett's Handedness Inventory (Annett, 1975). They had a mean duration of illness of 3.30 ($SD = 3.62$) years and an average age of onset of 24.80 ($SD = 9.77$) years. The average age of the subsample was 28.20 ($SD = 10.49$) years and they had an average

education of 12.70 ($SD = 3.09$) years. Estimated general intellect (PPVT-R) was in the low average range ($M = 94.90$, $SD = 20.10$). The subset was also similar to the general sample in positive ($M = 24.40$, $SD = 10.94$), negative ($M = 29.20$, $SD = 4.13$), and global ($M = 47.10$, $SD = 11.51$) symptomatology. Also, consistent with the general sample, the subset exhibited relatively minimal dyskinesia (*very mild*: $n = 1$; *mild*: $n = 1$) and parkinsonism (*very mild*: $n = 2$; *mild*: $n = 1$). The 2 patients exhibiting dyskinesia did not meet research diagnostic criteria for tardive dyskinesia at either baseline or follow-up testing. The subset included 4 patients who had been neuroleptic naive at their initial assessment and the washout periods of the remaining 6 patients were 7 days ($n = 3$), 16 days, 21 days, and 25+ days. Medication at the time of the second testing consisted of double blind risperidone or haloperidol ($n = 1$), double blind risperidone or haloperidol combined with benzotropine ($n = 2$), quetiapine ($n = 1$), risperidone ($n = 4$), risperidone combined with propranolol ($n = 1$), and olanzapine ($n = 1$).

Procedure

Participants with a clinical diagnosis of schizophrenia were referred for investigation by their AHE staff psychiatrist. After obtaining informed consent from the participant, the medical chart was reviewed and they were interviewed by the first author to confirm the diagnosis. During this interview, and blind to the psychometric results, symptoms of schizophrenia were quantified with the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1992) and extrapyramidal motor symptoms were assessed with the Extrapyramidal Syndrome Rating Scale (ESRS; Chouinard et al., 1990). The 21 normal controls recruited for the study also underwent a brief interview to screen for possible neurological or psychiatric disorder, current medications, and general health, but they were not rated on the PANSS or ESRS. The brief interview consisted of several structured questions that dealt with personal psychiatric history, general health, medication history, and motor function. Control subjects with a confirmed psychiatric diagnosis, a medical condition with motor involvement, or a current prescription for medication were excluded from participation. A well-trained psychology assistant blind to the medication status of the participant administered a psychological test battery that included Annett's Handedness Inventory (Annett, 1975), the Peabody Picture Vocabulary Test-Revised (PPVT-R; Dunn & Dunn, 1981), and an instrumental method for the quantification of hand force persistence (Caligiuri & Lohr, 1994). In this method isometric hand force is converted to electrical output by use of a rigid metal lever outfitted with resistive strain gauges, graciously provided to us by Michael Caligiuri, connected to an analog-digital converter (Bioamp 215, Biocommunication Electronics, Southfield, Michigan). Participants were seated in front of a computer monitor with the hand to be tested placed palm down on the base of a small, rectangular, wooden platform on which a

10 cm (L) \times 2 cm (W) \times 0.4 cm (H) metal lever was attached with an elevation of approximately 1 cm. Hand presentation was counterbalanced across subjects by using a random number table with even numbers corresponding to right hand tested first and odd numbers corresponding to left hand tested first. The participants positioned their index finger on the lengthwise dimension of the lever and the force applied by flexion at the metacarpophalangeal joint was transduced by the strain gauges at the terminal end of the lever. They were instructed to match for 20 s their force signal represented by a blue line on the monitor with a target signal represented by a horizontal red line calibrated to a force of 400 g. The hand being tested was never out of view and the force signal on the monitor provided constant visual feedback. A brief practice trial of approximately 15 s was followed by two 20-s trials with 15-s intertrial rest periods. All hand force testing was done on an IBM compatible workstation (100 MHz) computer running Snapmaster v3.0 (HEM data corporation, 1991-1994) operating under Microsoft Windows Version 3.0.

Analysis

Hand force persistence

Following digitization, the wave force signal for the entire procedure was divided into a linear series of 10-s epochs after excluding the practice and rest periods. Each epoch was then screened for outliers defined by responses less than 250 g of force or greater than 550 g of force. The first clean 10-s epoch from the first trial and the last clean 10-s epoch from the last trial were selected for analysis to diminish contributions from miscomprehension, maladaptation, or practice. This resulted in two sets of 1,000 continuous observations each representing 100 observations/s within a 10-s epoch. The standard deviation for each set of 1,000 observations was calculated and a mean of the two represented the dependent variable in the analyses reported below. Data were analyzed with parametric procedures (t tests) when Levene's test for homogeneity of variance was satisfied and with nonparametric procedures (Mann-Whitney and Wilcoxon) when this criterion was not met. The prospective analysis of treatment effects on hand-force persistence entailed a repeated measures analysis of variance with time (baseline vs. follow-up) and hand (right vs. left) entered as the within-group variables. All hand force error calculations and statistical analyses were performed with the Statistical Package for the Social Sciences v7.5 (SPSS, 1993).

RESULTS

The hypothesis that unmedicated schizophrenia patients would show an atypical asymmetry of hand force persistence was evaluated by computing a laterality index derived by subtracting the right hand force error from the left hand force error (see Figure 1). The laterality index met

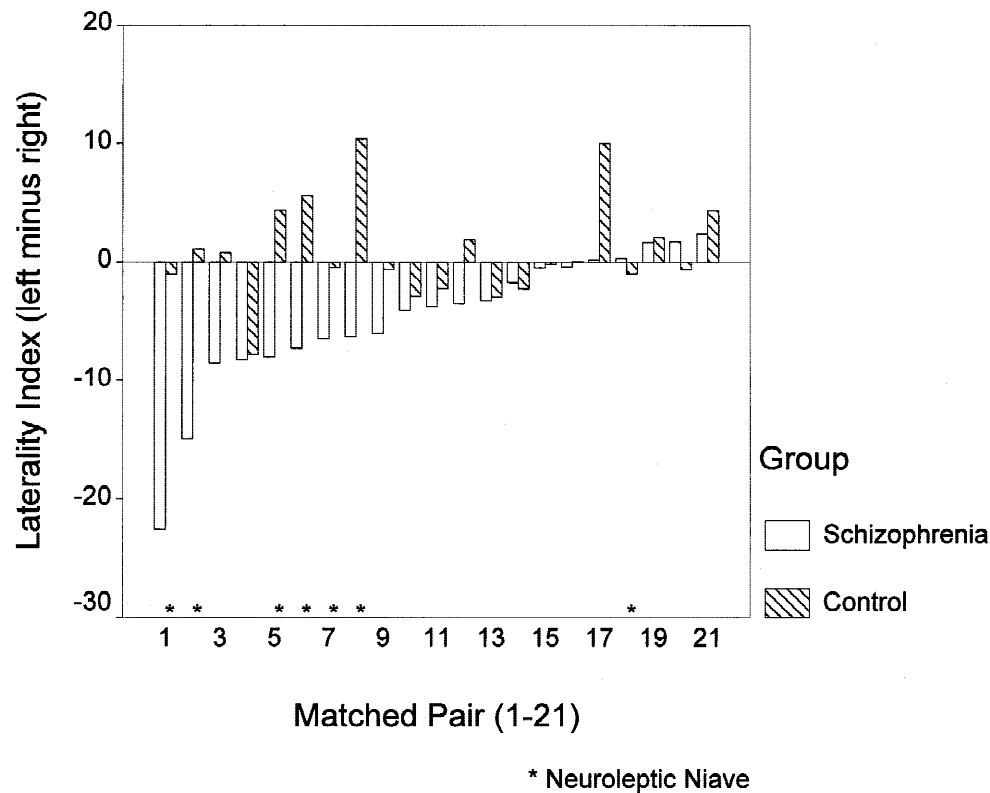


Fig. 1. Laterality index (L – R) for controls and unmedicated schizophrenia patients.

Levene's test for homogeneity of variance and hence a one-tailed t test for independent samples was used to compare the schizophrenia sample to the normal controls. A significant bias against the right hand relative to the left hand was apparent in the schizophrenia sample ($M = -4.73$, $SD = 5.95$) relative to the normal control sample [$M = 0.89$, $SD = 4.24$; $t(40) = 3.53$, $p = .0005$]. Subsidiary analyses showed the atypical asymmetry in the seven neuroleptic naïve schizophrenia patients ($M = -9.34$, $SD = 7.33$) relative to the matched controls [$M = 2.19$, $SD = 4.25$; $t(12) = 3.60$, $p = .002$] and in the remaining 14 previously medicated schizophrenia patients ($M = -2.43$, $SD = 3.54$) relative to their matched controls [$M = -.24$, $SD = 4.24$; $t(26) = 1.81$, $p = .042$]. The neuroleptic naïve sample showed a much greater asymmetry than the previously medicated sample of patients with schizophrenia [$t(19) = 2.95$, $p = .004$]. Thus, the anticipated atypical asymmetry was apparent in unmedicated patients with schizophrenia and it was most robust in patients with no prior exposure to neuroleptic treatment.

In an effort to further delineate the source of the atypical laterality in the patients with schizophrenia, additional analyses were conducted on the right and left hand force error scores (see Table 1). The variance for right hand force error scores was not equivalent between groups (Levene's $F = 10.06$, $p = .006$) and hence all hand force measures were analyzed with two-tailed nonparametric Mann-Whitney tests for independent sample comparisons and Wilcoxon signed

rank tests for paired comparisons. The right hand of the schizophrenia sample showed a significant impairment relative to the control sample ($z = -3.21$, $p = .001$), but the groups did not differ on the left hand ($z = -1.15$, $p = .23$). Within the schizophrenia sample, the right hand was impaired relative to the left hand ($z = -3.25$, $p = .001$), in contrast to the absence of a difference between hands within the normal control sample ($z = -.47$, $p = .64$). The atypical asymmetry of hand force in schizophrenia thus appears to be primarily related to diminished skill with the right hand.

Further analyses of the schizophrenia sample were undertaken to assess a contribution from previous medication exposure. The impairment of the right hand relative to the left hand was apparent in both the neuroleptic naïve sample ($z = 2.20$, $p = .028$), and the previously medicated sample ($z = 2.23$, $p = .026$), but not the normal control sample ($z = .47$, $p = .639$). Comparisons between groups showed a trend towards lower right hand performance in the neuroleptic naïve compared to the previously medicated sample ($z = 1.94$, $p = .052$), though the two groups showed no suggestion of a difference for the left hand ($z = .15$, $p = .881$). The neuroleptic naïve sample showed a significant impairment of the right hand relative to their matched control group ($z = 2.36$, $p = .018$), but no differences on the left hand ($z = .70$, $p = .482$). The previously medicated sample showed a trend towards more right hand deficit relative to the normal control group ($z = 1.93$, $p = .054$), and no difference on the left hand ($z = 1.01$, $p = .312$). The atypical asym-

Table 1. Hand force persistence in schizophrenia and normal controls

Group	Force Persistence Error (in grams of force)		
	Left hand <i>M</i> (<i>SD</i>)	Right hand <i>M</i> (<i>SD</i>)	Laterality index (L – R) <i>M</i> (<i>SD</i>)
Schizophrenia (<i>N</i> = 21)	8.86 (3.70)	13.59* (7.20)	–4.73** (5.95)
Controls (<i>N</i> = 21)	8.48 (5.19)	7.59 (3.03)	0.89 (4.23)

*Between groups, $p = .001$. Schizophrenia within group (left vs. right), $p = .001$.

**Between groups, $p = .0005$.

metry of hand force in schizophrenia is thus apparent in both neuroleptic naïve and unmedicated previously treated patients and an attribution of this asymmetry to right hand impairment receives strong support from the neuroleptic naïve sample but weaker support from the unmedicated previously treated sample.

A series of exploratory correlations were undertaken to examine possible relations of hand force persistence to baseline clinical symptoms of schizophrenia, vocabulary, and education. The restricted range of scores within the small number of patients exhibiting movement disorder precluded examination of associations between hand force persistence and motor syndromes. Aside from a marginal positive relationship between right hand force and PANSS negative scores (Pearson's $r = .32$, $p = .15$), there was little evidence to suggest a relationship between clinical symptoms and hand force persistence or hand force laterality (Pearson's r range = $-.24$ to $.25$, all $ps > .27$). Within the patient sample, education was unrelated to hand force but vocabulary test scores from the PPVT showed a significant association to the laterality index ($r = .54$, $p = .012$), marked by a significant inverse association to right hand force error ($r = -.62$, $p = .003$) and no significant association to left hand force error ($r = -.34$, $p = .132$). It is unlikely that an improved vocabulary results in better hand force persistence but it is possible that the diminished left hemisphere function detected by impairment of right hand force measure may be related to a lower vocabulary score.

From the results of the 2×2 ANOVA for the follow-up subset, an interaction between Hand \times Time was observed [$F(1, 18) = 8.15$, $p = .011$], and there was a main effect of hand [$F(1, 18) = 6.99$, $p = .017$]. As evident from Table 2,

the interaction resulted from a marked asymmetry at baseline [$t(9) = 2.97$, $p = .016$] that was not apparent after treatment [$t(9) = 0.28$, $p = .786$] because the right hand showed a substantial improvement with treatment [$t(9) = 3.82$, $p = .004$] that was not apparent with the left hand [$t(9) = 1.69$, $p = .126$]. Clinical status improved over the course of treatment on both the positive [baseline: $M = 24.40$, $SD = 10.94$; posttreatment $M = 12.60$, $SD = 5.04$; $t(9) = 4.11$, $p = .009$], and negative (baseline: $M = 29.20$, $SD = 4.13$; posttreatment: $M = 19.50$, $SD = 7.01$; $t(9) = 4.33$, $p = .002$) syndrome scales, but the improvement was unrelated to changes in hand force persistence (Pearson's r value range: $-.36$ – $.30$, all $ps > .31$). The correlation between duration of neuroleptic washout period and hand force improvement in the 6 previously treated patients was also not significant (right hand: $r = -.55$, $p = .26$; left hand: $r = -.022$, $p = .68$). Although the sample size was too small for statistical comparison, the improvement was suggested in both the neuroleptic naïve and previously treated patients.

DISCUSSION

A substantial asymmetrical deficit of right hand force persistence was apparent in the unmedicated schizophrenia sample and the asymmetry was mitigated after 4 weeks of neuroleptic treatment. The results are consistent with expectations derived from the one prior prospective examination of motor skill which showed a right sided deficit that also dissipated with neuroleptic treatment (Tan & Gurgun, 1986), as well as with the results of prior studies of unmedicated samples showing a left turning bias, excessive right hand tremor, and deficient right hand finger tapping speed

Table 2. Hand force persistence and neuroleptic treatment in schizophrenia

Group (<i>n</i> = 10)	Hand force persistence error (in grams of force)		
	Left hand <i>M</i> (<i>SD</i>)	Right hand <i>M</i> (<i>SD</i>)	Laterality index (L – R) <i>M</i> (<i>SD</i>)
Unmedicated baseline	8.67 (2.53)	14.94* (7.24)	–6.28 (6.69)
Neuroleptic retest	7.24 (2.03)	6.37† (2.20)	0.24** (2.73)

*Left hand vs. right hand, $p = .016$.

**Baseline vs. retest, $p = .011$.

†Baseline vs. retest, $p = .004$.

(Bracha, 1987; Caligiuri & Lohr, 1993; Gorynia & Uebelback, 1992). The results are also consistent with prior reports of asymmetrical hand force persistence error suggesting a relative right hand disadvantage in a neuroleptic naïve sample (Lohr & Caligiuri, 1995). It is thus reasonable to presume that the failure to detect a relative right hand motor deficit in prior studies of finger tapping (Ragland et al. 1999) and finger-thumb opposition (Walker & Green, 1982), may relate to the medication status of the patients previously evaluated. The present results also recapitulate our observations from two independent unmedicated samples showing a relative left nostril olfactory acuity deficit, and the dissipation of this asymmetry with the addition of neuroleptic treatment to one of the samples (Purdon & Flor-Henry, in press). There is thus evidence from psychometric assessments of both sensory and motor systems to implicate a left hemisphere dysfunction in unmedicated schizophrenia that is consistent with pathology observed with functional neuroimaging in unmedicated samples (Buchsbaum et al. 1992; Guenther et al., 1986b), and that may be improved with neuroleptic treatment.

The cerebral mechanism responsible for an asymmetry in the motor skills of unmedicated patients with schizophrenia could involve any sector within the subcorticothalamocortical motor function loop (Alexander et al. 1986). In this circuit, the basal ganglia receive input from most areas of the neocortex, including primary and supplementary motor regions, at the striatum prior to transmission via the putamen and pallidum to the thalamus where efferent fibers project back to the association motor cortex. The pathological region, however, is most likely to involve a system with asymmetrical architecture. Thus, although functional neuroimaging has implicated physiological abnormalities in the left primary and supplementary motor areas during contralateral movements (Buchsbaum et al. 1992; Guenther & Breiting, 1985; Guenther et al., 1986a, 1986b, 1994; Schroder et al., 1995), the left motor and association cortex has been implicated in bilateral limb movements in right-handed normal controls (Kolb & Whishaw, 1996). As such, it is difficult to assimilate a predominantly unilateral right-sided motor deficit with dysfunction of the left motor and association cortex. The right hand force persistence deficit observed in the present schizophrenia sample is also not in keeping with skilled movement impairments commonly seen after exclusive sensorimotor cortex damage (Donoghue & Sanes, 1994).

A unilateral subcortical pathology involving the neostriatum or the thalamus may provide a more reasonable explanation, particularly given prior reports of similar hand force impairments in neurological patients with basal ganglia lesions (Keele & Ivry, 1991) and a prior case report of a patient with right fine motor control impairment related to left striatonigral degeneration (Sullivan et al., 1991). Asymmetrical neurotransmitter distributions in schizophrenia, particularly in relation to dopaminergic hypofunction in left basal ganglia structures, have been cited as a neural basis for the motor asymmetries (Bracha, 1987; Caligiuri & Lohr,

1993; Jerussi & Taylor, 1982), and this view has received some support from observations in schizophrenia of left globus pallidum hypometabolism, abnormal increased volume of structures in the left striatum, and abnormal decreased volume of the left internal pallidum (see review by Bogerts et al., 1985; Seeman, 1992). Although pathology of the neostriatum could readily account for the motor asymmetry results, it provides a less efficient account of the asymmetry observed in sensory systems.

A more parsimonious account for the asymmetries observed in both the motor and the sensory systems may be provided by further delineation of pathology in the thalamus implicated by structural neuroimaging, functional neuroimaging, and postmortem studies (see review of Bogerts, 1993; Buchsbaum et al., 1996). The ventral lateral and ventral anterior nuclei of the thalamus are part of the extrapyramidal motor system and the lateral geniculate, medial geniculate, medial dorsal, and ventral posterior nuclei of the thalamus relay visual, auditory, olfactory, and haptic systems, respectively, all of which also seem to show a left hemisphere deficit in unmedicated patients that improves with neuroleptic treatment. Thus although a cortical pathology may not explain the unilateral nature of the motor impairment, and a neostriatum pathology may not provide a parsimonious account for both the motor and the sensory evidence, thalamic neuropathology of the left cerebral hemisphere is both consistent and parsimonious with the evidence to date. We are unaware of specific evidence for schizophrenia showing asymmetrical pathophysiology or treatment response in the thalamus but this would appear to be an important cerebral region for further study.

Neuroleptic treatment has a long association with induction of extrapyramidal movement disorders in schizophrenia and it is therefore remarkable that the elimination of the motor asymmetry in the present study resulted primarily from an improvement in right hand force persistence. However, with the possible exception of 3 patients under double-blind treatment conditions (risperidone or haloperidol), participants in the treatment arm were receiving one of three novel antipsychotic agents (quetiapine: $n = 1$; olanzapine: $n = 1$; risperidone: $n = 5$). There is sufficient evidence to suggest that these second generation neuroleptics are less likely than the first generation treatments to elicit extrapyramidal syndromes (see review by Andersson et al., 1998) and that the difference may relate to a diminished affinity for dopamine receptors in the neostriatum relative to the mesolimbic system (Farde et al., 1992; Gardner, 1992; Seeman, 1992). To some extent the improvement of motor skill may thus relate to a dissipation of the motor effects of residual prior treatments not entirely eliminated during our washout period, similar to the improvement in neurological soft signs observed after switching from a first to a second generation antipsychotic medication (Smith et al., 1999). However, the magnitude of the change was not related to the length of the washout period and advantages were also apparent for the neuroleptic naïve sample. It is therefore possible that the novel agents have a beneficial effect on

motor skill similar to the beneficial effect observed in sensory perception (Purdon & Flor-Henry, in press), and possibly related to the mechanism for changes in higher cognitive skills observed with the novel treatments (see reviews by Purdon, 1999, 2000, in press). There are, as yet, no studies of which we are aware showing asymmetrical benefits of the novel agents on neuropsychological assessments, but the well validated prominence of left cortical function in verbal skills and right cortical function in non-verbal skills may suggest additional valuable avenues for further research.

An asymmetry of motor and sensory skills in schizophrenia that is sensitive to antipsychotic treatment is of considerable value to further research toward an understanding of the behavioral manifestation of the cerebral basis for schizophrenia and the differential efficacy of various pharmacotherapeutic interventions. Additional study is warranted and this work may benefit from several potential limitations of the present experimental design. In the absence of alternate forms for the motor and sensory tasks described above, this type of research is often unable to entirely eliminate a potential contribution of practice effects from the primary benefit of atypical neuroleptic treatment. Although practice effects cannot be ruled out with complete confidence in the present study, the lack of improvement in left-hand performance and the limited amount of exposure to the task (two 20-s trials per hand separated by at least 30 days) tend to argue against this possibility. The observation of a similar shift in dichotic listening performance following medication reduction also tends to argue against this possibility in a more general context (Seidman et al., 1993). Also, although there was no difference between the retained and the nonretained participants on key demographic variables, we cannot rule out the possibility of a sample selection bias arising from the unavailability of some of our baseline sample for assessment after treatment. On a final methodological note, the association between estimated IQ and hand-force persistence will warrant further scrutiny, particularly in light of the lack of an association between education and hand-force persistence. Whereas this may suggest a contribution of vigilance and attention to both the intellectual and motor assessments that cannot be entirely ruled out from the present results, such an interpretation would not appear to provide an explanation for our observed differences in motor asymmetry, nor would it provide a cogent account for the previously reported differences in sensory asymmetry associated with schizophrenia. Thus, although it is unlikely that practice effects, sample selection bias, or general performance decrements have undermined the inferences drawn from the present results, further research in this area may benefit from a consideration of these factors.

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