ORIGINAL ARTICLE

Dysfunctional Neural Plasticity in Patients With Schizophrenia

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Context: Neural plasticity in the human cortex involves a reorganization of synaptic connections in an effort to adapt to a changing environment. In schizophrenia, dysfunctional neural plasticity has been proposed as a key pathophysiological mechanism.

Objective: To evaluate neural plasticity in unmedicated and medicated patients with schizophrenia compared with healthy subjects.

Design: Neural plasticity can be evaluated from the motor cortex in healthy subjects using transcranial magnetic stimulation through a paradigm known as use-dependent plasticity. This paradigm involves several steps: (1) measuring the spontaneous direction of transcranial magnetic stimulation–induced thumb movements; (2) training subjects to practice thumb movements opposite to this baseline direction for 30 minutes; and (3) measuring the direction of transcranial magnetic stimulation–induced thumb movement after training. Previous experiments have shown that in healthy subjects, posttraining transcranial magnetic stimulation–induced movements occur in a vector commensurate with the practiced movements, which may be associated with time-limited reorganization of motor circuits.

Setting: All of the participants were recruited and evaluated at the Centre for Addiction and Mental Health.

Participants: Fourteen medicated and 6 unmedicated patients with schizophrenia and 20 healthy subjects were recruited.

Main Outcome Measure: It was anticipated that patients with schizophrenia would demonstrate attenuated motor reorganization in the direction of training.

Results: Both medicated and unmedicated patients with schizophrenia demonstrated significantly reduced motor reorganization compared with healthy subjects.

Conclusions: It is possible that in schizophrenia, these deficits in neural plasticity are related to disturbances of γ-aminobutyric acid, *N*-methyl-D-aspartate neurotransmission, or dopamine that may potentially account for the aberrant motor performance of these patients.

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PLASTICITY IN THE HUMAN CORtex involves a reorganization of synaptic connections in an effort to adapt to a changing environment. Several neurobiological mechanisms have been shown to mediate neural plasticity. One such mechanism involves the unmasking of existent corticocortical connections[1] through the removal of cortical inhibitory neurotransmission.[2] For example, in humans, the administration of a drug that enhances γ-aminobutyric acid (GABA) activity (ie, lorazepam) disrupts plasticity,[3] whereas physiological plasticity following lower limb amputation likely occurs through a reduction in cortical GABAergic inhibition.[4] *N*-methyl-D-aspartate (NMDA) receptor–mediated neurotransmission has also been implicated in the development of plasticity. Activation of the NMDA receptor results in facilitation of long-term potentiation (LTP), a process that is essential for neuronal reorganization, learning, and memory.[5] As theorized by Hebb[6] in 1949, LTP is reflected as changes in synaptic strength in response to coincident activation of coactive cells, a process that depends in part on activation of double-gated NMDA receptors that serve as a "molecular" coincidence detector.[7,8] In fact, drugs that disrupt NMDA receptor–mediated neurotransmission have also been shown to disrupt neural plasticity.[3] Finally, it has also been demonstrated that dopamine (DA) subserves several key elements that mediate neural plasticity. In motor path-

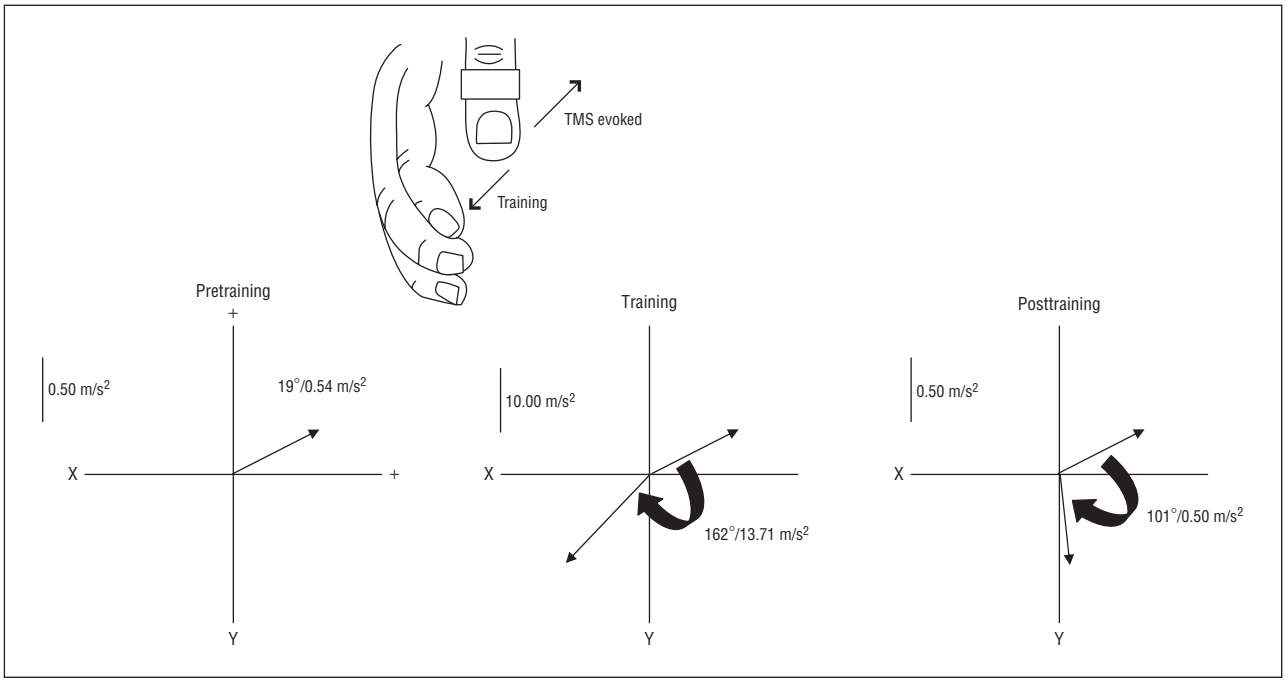

Figure 1. Accelerations in the x and y dimensions demonstrating use-dependent plasticity. Data are from 20 healthy subjects. Vectors represent both mean angles and movement accelerations. The x-axis represents abduction (+) and adduction (–). The y-axis represents extension (+) and flexion (–). Use-dependent plasticity is accomplished in several steps. In pretraining, the spontaneous direction of transcranial magnetic stimulation (TMS)–induced movement is measured. In training, individuals are trained to perform brisk thumb movements opposite to the direction of TMS-induced thumb movement. In posttraining, TMS is reapplied to the cortex while the direction of induced thumb movement is evaluated, and directional changes in thumb movement are evaluated over time. It is this process of orientation in the direction of the training movement that represents an index of neural plasticity.

ways, for example, striatal plasticity has been shown to be highly reliant on DA neurotransmission owing to the close connection between DA terminals and ionotropic glutamatergic receptors (ie, NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid [AMPA] receptors) on medium spiny neurons in which DA appears to regulate glutamate release as well as to control the opening, distribution, and anchoring of NMDA and AMPA receptors to cell membranes.[9,10] Additionally, NMDA activation of DA D_1 but not D_2 receptors appears to potentiate LTP in the cortex.[11]

Several lines of evidence suggest that the neurotransmitter mechanisms mediating plasticity in the cortex are disordered in schizophrenia (SCZ). For example, dysfunctional GABA and NMDA receptor–mediated neurotransmission have figured prominently in the pathophysiology of this disorder.[12-16] It follows, therefore, that disrupted neural plasticity may be a corollary to an alteration of these neurotransmitter mechanisms. In addition, genetic and postmortem studies implicated abnormalities in dysbindin, neuregulin, and reelin, proteins involved in synaptic plasticity, as possible contributors to SCZ pathological findings.[17-20] Disturbances in the aforementioned mechanisms are anticipated to result in changes in the strength of neuronal connectivity at either a cellular or network level because the strength of neuronal coupling is an important predictor as to whether such connections outlast developmental pruning in the cortex.[21,22] Collectively, the aforementioned lines of evidence suggest that SCZ is a disorder associated with disturbances in the neural processes that underlie neural plasticity. However, direct neurophysiological evidence demonstrating a disruption of the reorganizational processes that result in neural plasticity is lacking.

Use-dependent plasticity represents a neurophysiological paradigm to directly measure in vivo reorganizational processes that are involved in generating neural plasticity in the human motor cortex. This paradigm involves measuring the spontaneous direction of transcranial magnetic stimulation (TMS)–induced thumb movements prior to and after a 30-minute training period in which individuals perform thumb movements that are in a direction opposite to that at baseline. Specifically, use-dependent plasticity is accomplished in 4 steps (**Figure 1**): (1) the spontaneous direction of TMS-induced movements is measured; (2) individuals are then trained to perform a simple motor task opposite to the direction of TMS-induced thumb movement; (3) TMS is reapplied to the cortex while the direction of induced thumb movement is evaluated; and (4) directional changes in thumb movement are evaluated over time. Classen et al[23] demonstrated that immediately after training, the direction of TMS-induced movements follows the direction of training. It is this process of orientation in the direction of the training movement that represents an index of neural plasticity. These reorganizational processes that occur as part of thumb reorientation in the direction of training may also represent a form of neurophysiological learning that takes place primarily in the motor cortex. Therefore, the objective of this study was to evaluate neural plasticity through the use-dependent plasticity paradigm in patients with SCZ and healthy subjects. It was hypothesized that patients with SCZ would demonstrate deficient neural plasticity compared with healthy

Table 1. Medications Received by Medicated Patients With Schizophrenia

Patient No.	Medication	Dosage, mg/d
1	Olanzapine	15
2	Olanzapine	20
3	Quetiapine fumarate	400
4	Risperidone	3
5	Olanzapine	15
6	Olanzapine	20
7	Risperidone	7
8	Olanzapine	10
9	Quetiapine fumarate	700
10	Quetiapine fumarate	900
11	Olanzapine	12.5
12	Ziprasidone hydrochloride	80
13	Olanzapine	10
14	Olanzapine	10

Table 2. Demographic and Clinical Characteristics of the Study Participants

Characteristic	Healthy Subjects With No Psychiatric Illness[a] (n=20)	Medicated Patients With Schizophrenia[a] (n=14)	Unmedicated Patients With Schizophrenia[a] (n=6)
Age, mean (SD), y	30.50 (7.52)	32.57 (11.71)	32.67 (9.67)
Sex, No.			
Female	6	4	2
Male	14	10	4
PANSS scores, mean (SD)			
Total	NA	70.14 (11.53)	68.17 (9.52)
Positive	NA	16.14 (3.23)	15.83 (2.40)
Negative	NA	21.64 (3.82)	18.33 (2.88)
General	NA	32.36 (7.08)	34.00 (5.73)
AIMS score, mean (SD)	NA	0.71 (2.13)	0 (0)
SAS score, mean (SD)	NA	0.64 (1.08)	0.50 (1.22)
BAS score, mean (SD)	NA	0.43 (0.83)	0.83 (2.04)

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; BAS, Barnes Akathisia Scale; NA, not applicable; PANSS, Positive and Negative Syndrome Scale; SAS, Simpson-Angus Scale.
[a] Confirmed by the Structured Clinical Interview for *DSM-IV*.

subjects and that such deficits would not be accounted for by deficient training performance or by treatment with antipsychotic medications.

METHODS

PARTICIPANTS

This study included 20 right-handed patients (confirmed using the Oldfield Handedness Inventory[24]) with a *DSM-IV* diagnosis of either SCZ or schizoaffective disorder confirmed by the Structured Clinical Interview for *DSM-IV*.[25] Of the 20 patients, 6 were antipsychotic free for 1 month or longer and 14 were medicated with a single atypical antipsychotic medication alone (**Table 1**). The control group consisted of 20 healthy, right-handed volunteers. Patient and healthy subject groups were similar across all of the demographic variables (**Table 2**). Healthy subjects were screened for psychopathological findings with a modified Structured Clinical Interview for *DSM-IV*.[25] Exclusion criteria included a self-reported comorbid medical or neurological illness, a history of drug or alcohol abuse, or concurrent treatment with any central nervous system–active medications. In patients with SCZ, motor abnormalities were assessed using the Abnormal Involuntary Movements Scale,[26] the Simpson-Angus Scale,[27] and the Barnes Akathisia Scale[28] prior to neurophysiological investigation. The research ethics board at the Centre for Addiction and Mental Health approved the study and written informed consent was obtained for each participant.

ELECTROMYOGRAPHY RECORDING

Surface electromyography was recorded from the right abductor pollicis brevis (APB) with disposable disc electrodes placed in a tendon-belly arrangement over the bulk of the APB and the first metacarpal-phalangeal joint. The forearm and digits 2 through 5 were isolated in a plastic splint to prevent any forearm movement while the thumb was allowed to move freely. The signal was amplified (model 2024F; Intronix Technologies Corp, Bolton, Ontario, Canada), filtered (band pass 2 Hz to 2.5 kHz), digitized at 5 kHz (Micro 1401; Cambridge Electronic Design, Cambridge, England), and stored in a laboratory computer for offline analysis.

TMS PROCEDURE

Subjects were seated in a comfortable chair. Transcranial magnetic stimulation of the left motor cortex was performed with a 7-cm figure-eight coil and a Magstim 200 stimulator (Magstim Co, Whitland, Wales). The coil was placed at the optimal position for eliciting motor-evoked potentials from the right APB. The optimal position was marked on the scalp with a felt pen to ensure identical placement of the coil throughout the experiment. The handle of the coil pointed backward and was perpendicular to the presumed direction of the central sulcus, about 45° to the midsagittal line. The coil was held in position by a metal stand and the coil position was visualized constantly to ensure that it did not move from the optimal location for eliciting activation of the APB. The direction of the induced current was from posterior to anterior, optimal to activate the motor cortex transsynaptically.[29]

RESTING MOTOR THRESHOLD

The resting motor threshold, expressed as a percentage of maximum stimulator output, was measured by approaching from slightly suprathreshold intensities and determined to the nearest 1% of stimulator output. The resting motor threshold was defined as the lowest intensity that produced a motor-evoked potential greater than 50 μV in 5 of 10 trials in the relaxed APB.[30]

USE-DEPENDENT PLASTICITY

Use-dependent plasticity was measured according to the methods outlined by Classen et al.[23] Thumb direction and acceleration were measured with 2 single-axis accelerometers (Entran Inc, Fairfield, New Jersey) that were mounted on the distal phalanx of the thumb using a flat wooden platform. Accelerometers were positioned with one accelerometer oriented to record flexion and extension movements and the other oriented to record abduction and adduction movements. The accelerometer signals were amplified 200 times using amplifiers (Calex

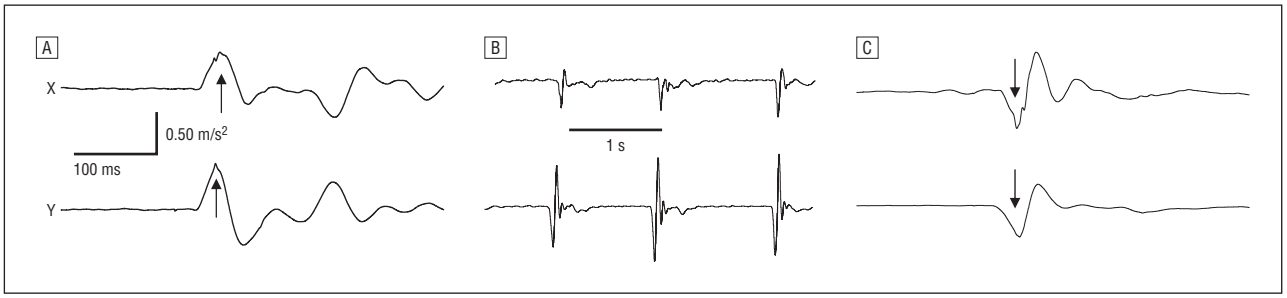

Figure 2. Movement accelerations from a single subject. The traces represent the averaged waveforms from a single healthy subject. A, Average acceleration in response to transcranial magnetic stimulation at baseline. B, Thumb accelerations in a direction approximately 180° to and opposite of the baseline movement direction. These training movements were paced using an analog metronome for 30 minutes at a frequency of 1 Hz and were carefully monitored by the investigators throughout the course of training. C, Immediately after training, the direction of transcranial magnetic stimulation–evoked movements follows the direction of training.

Mfg Co, Inc, Concord, California) and data were collected with an analog-digital interface (Micro 1401) using dedicated software (Signal; Cambridge Electronic Design).

RESTING MOVEMENT THRESHOLD AND STIMULATION INTENSITY

The resting movement threshold was defined as the lowest intensity necessary to produce an acceleration of 0.09 m/s^2 in 1 axis.[23] The stimulation intensity used was the lowest intensity necessary to produce consistent thumb movements in 1 axis.

EXPERIMENTAL PROTOCOL

In all of the subjects, the resting motor threshold, resting movement threshold, and stimulation intensity were determined in order. If consistent thumb movements were obtained, then the remainder of the experimental protocol was pursued. The baseline directions of TMS-evoked movements in the 2 orthogonal vectors (ie, flexion and extension as well as abduction and adduction) were derived by delivering TMS stimuli to the hand area of the motor cortex at a frequency of 0.1 Hz for 10 minutes (ie, 60 stimuli) (**Figure 2**A). All of the subjects were instructed to remain completely relaxed during this part of the experiment, surface electromyography activity was monitored from the APB at all times to ensure relaxation, and auditory feedback was given to subjects through a loudspeaker.

Following the determination of these baseline movement vectors, subjects were instructed to produce thumb movements in a direction that was approximately 180° to and opposite of the baseline movement direction. These training movements were paced using an analog metronome for 30 minutes at a frequency of 1 Hz and were carefully monitored by the investigators throughout the course of training (Figure 2B). To ensure adequate training performance, subjects were instructed to produce brisk thumb movements in the direction of training and to allow the thumb to rest immediately afterward without producing voluntary movements that would return the thumb back to its baseline position. These instructions were frequently repeated to ensure attention to the task as previously described.[23] The electromyography was monitored to ensure that this was done successfully. Approximately 8 training movements were recorded every minute (ie, 240 total or 13.33%) during the course of the 30-minute training period to determine the effectiveness of training movements, which was ascertained by evaluating both the acceleration and direction of these brisk movements.

Immediately after training, the directions of TMS-evoked movements were analyzed during the course of 30 minutes (Figure 2C). Again, TMS stimuli were delivered to the hand area of the motor cortex at a frequency of 0.1 Hz at the intensity used before training. Any trials that were contaminated with motor activity were discarded prior to analysis.

STATISTICAL ANALYSIS

Groups were compared using repeated-measures analysis of variance. Group membership (ie, patients or subjects) was entered as a between-group independent variable. The posttraining interval (eg, 0, 10, 20, and 30 minutes) was entered as the within-group independent variable. The differences between the orientations of the TMS-induced movement of the thumb at baseline and after training served as the dependent variable. Single-variable differences between 3 groups were analyzed using a 1-way analysis of variance. Finally, a Pearson correlation coefficient was used to determine the relationship between variables. All of the statistical procedures were 2-tailed and significance was set at $\alpha = .05$. All of the analyses were computed using SPSS version 10.0 statistical software (SPSS Inc, Chicago, Illinois) and conducted by one of us (Z.J.D.).

RESULTS

All of the subjects tolerated the protocol without any adverse events. A total of 7 trials were discarded out of 9600 trials recorded in the entire sample. In 4 healthy subjects, 1 trial was discarded in the pretraining period and 4 trials were discarded in the posttraining period. By contrast, in 2 medicated patients, 2 trials were discarded in the posttraining period. Therefore, 0.07% of trials were discarded, all owing to incomplete muscle relaxation. The trials were discarded immediately following data collection.

RESTING MOTOR THRESHOLD, RESTING MOVEMENT THRESHOLD, AND STIMULATION INTENSITY

There was no significant difference in the resting motor threshold across groups (mean [SD] resting motor threshold: healthy subjects, 41.70% [6.57%] of stimulator output; medicated subjects, 43.61% [7.75%] of stimulator output; unmedicated subjects, 44.83% [7.52%] of stimulator output).

There was no significant difference in the resting movement threshold across groups (mean [SD] resting movement threshold: healthy subjects, 47.35% [7.21%] of

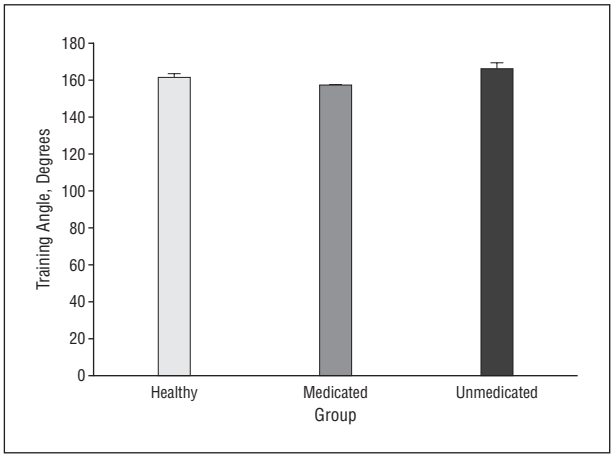

Figure 3. Training angles in 20 healthy subjects and 20 patients with schizophrenia (14 medicated and 6 unmedicated). Training angles represent 1 measure of the effectiveness of training. Each measure is expressed as a mean (standard error). There were no significant between-group differences in the ability to produce effective training movements that were directed approximately 180° to those at baseline.

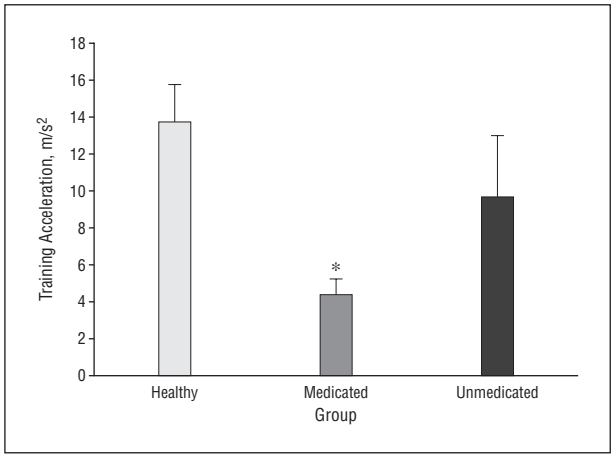

Figure 4. Training accelerations in 20 healthy subjects and 20 patients with schizophrenia (14 medicated and 6 unmedicated). Training accelerations represent a second measure of the effectiveness of training. Each measure is expressed as a mean (standard error). Medicated patients with schizophrenia demonstrated a statistically significant reduction in training accelerations compared with healthy subjects (*P=.001), but unmedicated patients did not.

stimulator output; medicated subjects, 49.38% [9.29%] of stimulator output; unmedicated subjects, 50.00% [7.21%] of stimulator output). Across all of the subjects, the movement threshold was on average 5.62% of stimulator output higher than the motor threshold.

There was also no significant difference in the stimulation intensity necessary to produce isolated and consistent thumb movements across groups (mean [SD] stimulation intensity: healthy subjects, 55.20% [9.41%] of stimulator output; medicated subjects, 56.46% [9.08%] of stimulator output; unmedicated subjects, 57.50% [8.64%] of stimulator output). Across all of the subjects, the stimulator intensity necessary to produce consistent thumb movements was on average 7.54% of stimulator output higher than the movement threshold.

BASELINE TMS-INDUCED ACCELERATIONS

The mean (SD) TMS-induced accelerations for healthy subjects were 0.54 (0.27) m/s^2 and 0.59 (0.37) m/s^2 at 10 and 5 minutes before TMS, respectively. In medicated patients with SCZ, the mean (SD) TMS-induced accelerations were 0.54 (0.28) m/s^2 and 0.53 (0.25) m/s^2 at 10 and 5 minutes before TMS, respectively. In unmedicated patients with SCZ, the mean (SD) TMS-induced accelerations were 0.52 (0.13) m/s^2 and 0.56 (0.21) m/s^2 at 10 and 5 minutes before TMS, respectively. There were no significant between-group differences in stimulation-induced acceleration across these 3 groups.

TRAINING

Training effectiveness was evaluated through both the accuracy of the training angle and the "briskness" or acceleration of training movements. The accuracy of the training angle was similar across all of the 3 groups of subjects (**Figure 3**). Vis-à-vis, training acceleration (**Figure 4**) between-group differences were found ($F_{2,37}$=6.32, P=.004) and post hoc tests (least significant difference) revealed a significant difference between medicated patients compared with healthy subjects (P=.001) but not between unmedicated and medicated groups (P=.16) or between unmedicated and healthy groups (P=.26). All of the subjects demonstrated minimal motor abnormalities (Table 2) and there was no relationship between motor abnormalities and training effectiveness.

POSTTRAINING ORIENTATION

The degree to which thumb direction oriented in the direction of training was evaluated in three 10-minute blocks during a total of 30 minutes. The dependent variable of interest was the mean angular displacement for each 10-minute block compared with baseline. Data are presented in **Figure 5**. A repeated-measures analysis of variance revealed a significant main effect for group ($F_{2,37}$=4.65, P=.02) (ie, healthy subjects, medicated patients with SCZ, and unmedicated patients with SCZ) with no group × time interactions. Post hoc tests (least significant difference) revealed a significant difference between unmedicated and healthy subjects (P=.04) (effect size, Cohen d=0.89)[31] and between medicated and healthy subjects (P=.01) (effect size, Cohen d=0.90) but not between medicated and unmedicated patients (P=.87). We found no association between training direction or training accelerations and posttraining orientation across all of the subjects. Finally, there was no relationship between motor abnormalities and posttraining orientation.

POSTTRAINING TMS ACCELERATIONS

A repeated-measures analysis of variance revealed no significant main effect for group and no group × time interactions, indicating that unmedicated and medicated patients did not differ significantly compared with healthy subjects on TMS-induced movement amplitudes following training. This suggests that the excitability of the cortex following training did not differ significantly between groups.

Our results demonstrate that both unmedicated and medicated patients with SCZ have significant deficits in neural plasticity as reflected by a failure of posttraining movements to orient in the direction of training compared with healthy subjects. Although medicated patients demonstrated significantly lower training accelerations compared with healthy subjects, there was no association between motor acceleration and posttraining orientation in the direction of the training movement. Moreover, unmedicated patients with SCZ had training accelerations similar to those of healthy subjects, suggesting that use-dependent plasticity deficits could not be accounted for by differences in the training itself. As use-dependent plasticity may be related to the inability to reorganize cortical synaptic connections required for movement reorientation in the direction of training, our results suggest that the neurophysiological mechanisms involved in such reorientation are disrupted in SCZ.

Several studies have examined the neurophysiological mechanisms responsible for use-dependent plasticity. One such mechanism may be LTP, which is represented by increases in postsynaptic neuronal activity secondary to repeated and contemporaneous activation of presynaptic neurons.[6] This process depends in part on activation of double-gated NMDA receptors that serve as molecular coincidence detectors. In use-dependent plasticity, repetitive training movements during a 30-minute period should result in reinforcement of a novel set of synaptic connections and concomitant orientation in the posttraining direction. In fact, Bütefisch et al[3] demonstrated that blockade of NMDA receptors using dextromethorphan resulted in significant disruption to posttraining orientation, furthering the link between NMDA receptor–mediated neurotransmission and the processes involved in LTP.

Modulation of GABAergic mechanisms has also been shown to have important effects on such use-dependent plasticity. Conceptually, plasticity may occur through the unmasking of latent corticocortical connections through the removal of inhibition as mediated by GABA inhibitory neurotransmission.[1,2] In this latter regard, it would be anticipated that either potentiation or disruption of GABAergic neurotransmission would alter such mechanisms as the processes involved in the formation and suppression of synaptic connections would be disrupted. Bütefisch et al[3] also demonstrated that the administration of lorazepam, a $GABA_A$ receptor positive allosteric modulator, resulted in a disruption of use-dependent plasticity with an effect similar to that of dextromethorphan. Collectively, these data suggest that both GABA and glutamate mechanisms are associated with use-dependent plasticity.

Both NMDA and GABA receptor–mediated neurotransmission have been implicated in the pathophysiology of SCZ. For example, it has been demonstrated that blockade of NMDA receptor–mediated neurotransmission is associated with worsening of psychosis in patients with SCZ[32] and produces behaviors in healthy subjects that are similar to the positive and negative symptoms

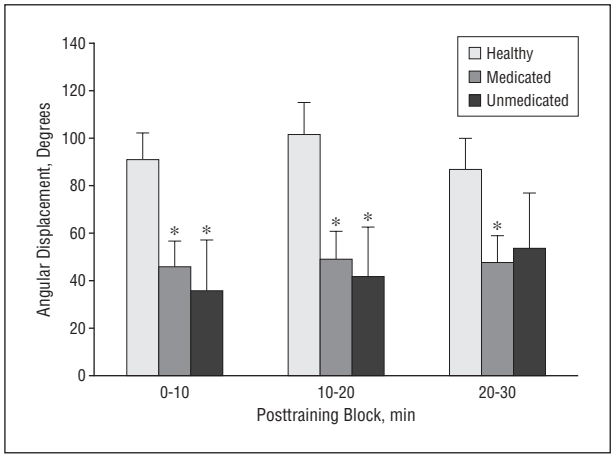

Figure 5. Posttraining orientation in 20 healthy subjects and 20 patients with schizophrenia (14 medicated and 6 unmedicated). The degree to which thumb direction oriented in the direction of training was evaluated in three 10-minute blocks during a total of 30 minutes. The dependent variable of interest was the mean angular displacement for each 10-minute block compared with baseline. Each measure is expressed as a mean (standard error). Our data demonstrate a significant difference between unmedicated and healthy subjects ($P=.04$) (effect size, Cohen $d=0.89$)[31] and between medicated and healthy subjects ($P=.01$) (effect size, Cohen $d=0.90$) but not between medicated and unmedicated patients ($P=.87$), suggesting that both patient groups do not orient in the direction of training as effectively as healthy subjects. *Significantly different compared with healthy subjects.

experienced by patients with SCZ.[33] Moreover, neuroanatomical[13] and neurophysiological evidence[15,16,34] suggests that both a decrease and a disruption of cortical GABAergic inhibitory neurotransmission is associated with the pathophysiological findings of SCZ. It is also important to note that these 2 neurotransmitter systems closely interact. That is, if either NMDA receptors or the GABAergic neurons that possess these receptors are missing or impaired, the newly formed circuits would be uninhibited resulting in excessive cortical stimulatory activity, a process that could potentially produce psychotic symptoms and structural brain changes.[14] This is in part because the NMDA receptor is extensively found on GABAergic interneurons and its activation provides tonic inhibitory control of pyramidal neurons (for review, see the article by Olney and Farber[14]). Collectively, these lines of evidence suggest that the deficits in both NMDA and GABA receptor–mediated neurotransmission may be associated with the neurobiological deficits that translate into disrupted use-dependent plasticity in SCZ.

The use-dependent plasticity paradigm may represent a neurophysiological process that underlies motor learning. By inference, therefore, impaired use-dependent plasticity in SCZ could account for the plethora of evidence suggesting that patients with SCZ demonstrate an inability to learn complex motor skills. For example, studies suggest that patients with SCZ show impaired motor learning as indexed through the rotary pursuit task.[35] More broadly, it has been reported that SCZ is associated with complex motor abnormalities, many of which present prior to the development of psychotic symptoms. In fact, Walker et al[36] have demonstrated that motor incoordination, clumsiness, and choreoathetosis occur at a much higher frequency in children going on to develop SCZ compared with their unaffected healthy counterparts. Also, retrospective

examination of case records from the preneuroleptic era indicated a movement disorder rate of 15% to 28%.[37,38] It has been suggested that such motor abnormalities arise out of aberrant DA projections to the motor cortex.[36] In fact, Benes et al[39] have reported a shift of dopaminergic terminations from pyramidal to nonpyramidal cells (ie, GABAergic inhibitory interneurons) in the cortex of patients with SCZ. In such circumstances, it would be anticipated that DA activation of D_2 receptors on GABAergic inhibitory interneurons would result in inhibitory deficits and, as a corollary, disruption of physiological plasticity. Further, imaging studies have demonstrated aberrant blood oxygen level–dependent premotor activation after 1 week of motor training compared with healthy subjects,[40] suggesting disrupted cortical circuitry in this disorder. It is possible, therefore, that this disruption in the ability of the cortex to learn such simple training movements as demonstrated through the use-dependent plasticity may arise out of aberrant DA neurotransmission and be responsible for motor impairments in this disorder.

There are some limitations in this study. The first relates to the fact that while our study provides compelling evidence to suggest that use-dependent plasticity is disrupted in SCZ, it is only suggestive of both LTP and motor learning abnormalities. Studies designed to pharmacologically manipulate such parameters to enhance or reduce plasticity directly in patients with SCZ would provide more direct evidence for a disruption of these neurophysiological processes. A second limitation is that this study involved a relatively small sample, particularly of unmedicated patients. Despite the fact that significant deficits were found, it is important that such disruption be replicated in a larger sample of patients to minimize error rates and stabilize statistical parameter estimates.[41] A third limitation is related to the cross-sectional nature of the study, a design that does not permit the evaluation of medication effects on use-dependent plasticity over time. A within-subject comparison incorporating a longitudinal design (ie, prior to and after treatment) would be a powerful validation of the link between use-dependent plasticity, the pathophysiological findings of SCZ, and the effects of antipsychotic medications. Potentially, such experiments could help to rule out the possibility of a medication-induced disruption on use-dependent plasticity or, by contrast, annex a relatively novel treatment target that may be a neurophysiological precursor to more complex cognitive processes that are involved in coordinating learning and memory or, perhaps, conceptual fluidity. A fourth limitation is that this paradigm captures relatively simple movements that may not adequately represent the full spectrum of motor dysfunction (eg, impairment in motor skill learning), which has been demonstrated in this disorder. These data therefore provide only indirect evidence to account for motor learning dysfunction and perhaps the cognitive impairment that compose part of the symptoms of the disorder.

In conclusion, our findings suggest that patients with SCZ demonstrate abnormalities in use-dependent plasticity. We contend that such abnormalities may be related to dysfunctional neurophysiological brain processes, including LTP, that exist as a result of disturbances of GABA, NMDA, or DA neurotransmission. We also suggest that these findings potentially account for the aberrant motor performance demonstrated in patients with SCZ. Future studies directly evaluating the link of use-dependent plasticity with motor performance and motor learning as well as directly evaluating the neurotransmitter systems involved in such processes are required to further our understanding of the neurophysiology of SCZ.

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