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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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 D1 but not D2 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 brisk thumb movements 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 directional changes in thumb movement are evaluated over time. Classen et al23 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 controls.

![Figure 1](http://archpsyc.jamanetwork.com/pdfaccess.ashx?url=/data/journals/psych/11860/ on 06/22/2017)
were medicated with a single atypical antipsychotic medi-
cation 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 find-
ings with a modified Structured Clinical Interview for
DSM-IV.20 Exclusion criteria included a self-reported comorbid med-
cal 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
Scale28 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 abduc-
tor 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 fore-
amow movement while the thumb was allowed to move freely.
The signal was amplified (model 2024F; Intronix Technolo-
gies Corp, Bolton, Ontario, Canada), filtered (band pass 2 Hz
from 2.5 kHz), digitized at 5 kHz (Micro 1401; Cambridge Elec-
tronic Design, Cambridge, England), and stored in a labora-
tory computer for offline analysis.

TMS PROCEDURE
Subjects were seated in a comfortable chair. Transcranial mag-
netic stimulation of the left motor cortex was performed with a
7-cm figure-eight coil and a Magstim 200 stimulator (Mag-
stim 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 left
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 con-
tantly to ensure that it did not move from the optimal loca-
tion 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 max-
imum stimulator output, was measured by approaching from
slightly suprathreshold intensities and determined to the near-
est 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 meth-
ods outlined by Classen et al.23 Thumb direction and accelera-
tion were measured with 2 single-axis accelerometers (Entran
Inc, Fairfield, New Jersey) that were mounted on the distal pha-
lax of the thumb using a flat wooden platform. Accelerom-
eters were positioned with one accelerometer oriented to rec-
ord flexion and extension movements and the other oriented
to record abduction and adduction movements. The accel-
rometer signals were amplified 200 times using amplifiers (Calex

Table 1. Medications Received by Medicated Patients With Schizophrenia

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

Table 2. Demographic and Clinical Characteristics of the Study Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Healthy Subjects</th>
<th>Medicated Patients With Schizophrenia</th>
<th>Unmediated Patients With Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>30.50 (7.52)</td>
<td>32.57 (11.71)</td>
<td>32.67 (9.67)</td>
</tr>
<tr>
<td>Sex, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>PANSS scores, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>NA</td>
<td>70.14 (11.53)</td>
<td>68.17 (9.52)</td>
</tr>
<tr>
<td>Positive</td>
<td>NA</td>
<td>16.14 (3.23)</td>
<td>15.83 (2.40)</td>
</tr>
<tr>
<td>Negative</td>
<td>NA</td>
<td>21.64 (3.82)</td>
<td>18.33 (2.88)</td>
</tr>
<tr>
<td>General</td>
<td>NA</td>
<td>32.36 (7.08)</td>
<td>32.57 (11.71)</td>
</tr>
<tr>
<td>AIMS score, mean (SD)</td>
<td></td>
<td>0.71 (2.13)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>SAS score, mean (SD)</td>
<td></td>
<td>0.46 (1.08)</td>
<td>0.50 (1.22)</td>
</tr>
<tr>
<td>BAS score, mean (SD)</td>
<td></td>
<td>0.43 (0.83)</td>
<td>0.83 (2.04)</td>
</tr>
</tbody>
</table>

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; BAS, Barnes Akathisia Scale; NA, not applicable; PANSS, Positive and Negative Syndrome Scale; SAS, Simpson-Angus Scale.

aConfirmed by the Structured Clinical Interview for DSM-IV.

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; BAS, Barnes Akathisia Scale; NA, not applicable; PANSS, Positive and Negative Syndrome Scale; SAS, Simpson-Angus Scale.

METHODS

PARTICIPANTS

This study included 20 right-handed patients (confirmed using the Oldfield Handedness Inventory25) with a DSM-IV diagno-
sis of either SCZ or schizoaffective disorder confirmed by the
Structured Clinical Interview for DSM-IV.23 Of the 20 pa-
tients, 6 were antipsychotic free for 1 month or longer and 14
were medicated with a single atypical antipsychotic medica-

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The resting movement threshold was defined as the lowest intensity necessary to produce an acceleration of 0.09 m/s² in 1 axis. 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). 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. C, Immediately after training, the direction of transcranial magnetic stimulation–evoked movements follows the direction of training.

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.

RESULTS

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...
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 x 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)^2 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 ACCELERATIONS

A repeated-measures analysis of variance revealed no significant main effect for group and no group x 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. 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 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. 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 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 and produces behaviors in healthy subjects that are similar to the positive and negative symptoms experienced by patients with SCZ. Moreover, neuroanatomical and neurophysiological evidence 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, 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. 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). 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. 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 have demonstrated that motor incoordination, clumsiness, and choreaathetosis occur at a much higher frequency in children going on to develop SCZ compared with their unaffected healthy counterparts. Also, retrospective

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) 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.
examination of case records from the preneuroleptic era indicated a movement disorder rate of 15% to 28%. It has been suggested that such motor abnormalities arise out of aberrant DA projections to the motor cortex. In fact, Benes et al. have reported a shift of dopaminergic terminations from pyramidal to nonpyramidal cells (i.e., GABAergic inhibitory interneurons) in the cortex of patients with SCZ. In such circumstances, it would be anticipated that DA activation of D2 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, 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. 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 (i.e., 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 (e.g., 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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Author Contributions: Dr Daskalakis had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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