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ScienceDirect
Schizophrenia Research 93 (2007) 334–344
SCHIZOPHRENIA RESEARCH
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Transcranial Magnetic Stimulation at M1 disrupts cognitive networks in schizophrenia

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Received 31 January 2007; accepted 1 February 2007
Available online 12 April 2007

Abstract

Transcranial Magnetic Stimulation (TMS) is rapidly gaining acceptance as a non-invasive probe into brain functionality. We utilize TMS to study the connectivity of a simple motor network in patients of schizophrenia ($N=19$), and in healthy control subjects ($N=9$). TMS was used in an externally paced finger tapping task, perturbing the internal network oscillations invoked by the finger motion as it keeps pace with a metronome. TMS perturbations were synchronized to the metronome and applied to the network at the level of the primary motor cortex (M1). Contrary to initial expectations, TMS did not affect the sensorimotor synchronization of subjects with schizophrenia or their tapping accuracy. TMS did cause extreme deviations in the finger's trajectory, and altered the timing perceptions of subjects with schizophrenia. Additionally, it invoked high-level deficiencies related to attention and volition in the form of lapses, implying that the connectivity between modules in the brain that underlie motor control, sensorimotor synchronization, timing perception and awareness of action, can be disrupted by TMS in subjects with schizophrenia, but not in healthy subjects. The ability to disrupt high level network functions with perturbations to the lower level of M1 supports models describing deficits in connectivity of distributed networks in the brains of schizophrenia patients. It also demonstrates the use of TMS to probe connectivity between components of such networks.

Keywords: Transcranial Magnetic Stimulation; Schizophrenia; Timing; Motor control; Cognition; Perception

1. Introduction

Leading theories in schizophrenia posit that different symptoms of the disease are caused by both a breakdown of connectivity between distributed brain circuits that underlie the fundamental cognitive and psychomotor functions, and the opposite extreme of over-connectivity (Friston, 1998). In particular, the 'Cognitive Dysmetria' model points to abnormal inter-regional connectivity within the cortico–cerebellar–thalamo–cortical circuit due to cerebellar dysfunction (Andreasen et al., 1996; Daskalakis et al., 2005; Ho et al., 2004). Dysfunction in this circuit is thought to disrupt synchrony, coordination, and timing of mental processes (Andreasen et al., 1999).

It is particularly instructive to study such disruptions using the network underlying an externally paced finger tapping task, since it combines sensorimotor coordination and synchrony with aspects of timing and time perception. Although a simple task, the neural network invokes

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doi:10.1016/j.schres.2007.02.019

sensory input, motor control, event timing, error correction and higher executive functions that interact in a timed, repetitive fashion. Surprisingly few studies have checked the performance of schizophrenia patients in this synchronization task, and those that did, found only that medicated schizophrenia patients were deficient in the motor synchrony of this task (Manschreck et al., 1981, 1985).

In this paper we studied the network's function by creating a periodic, precisely controlled external perturbation to the internal periodic process. We used Transcranial Magnetic Stimulation (TMS) to intervene in the oscillatory motion created by the internal circuitry activated by the finger-tapping task. TMS pulses were synchronized with a metronome and applied to the network at the level of the primary motor cortex, while the subject tried to tap to the beat. We hypothesized that differences between healthy and schizophrenia patients in neural network connectivity would manifest themselves as differences in the effects of the TMS perturbations on activity governed by the network.

We have recently shown (Levit-Binnun et al., in press) that TMS pulses to M1 during paced finger tapping had a great impact on the finger trajectory, without hindering the accuracy in timing in healthy subjects. The use of TMS in that study revealed that timing and motor components are distinct and separable in healthy subjects. Since timing deficits are known to exist in schizophrenia patients (Davalos et al., 2003; Elvevag et al., 2003) we expected to find in the present work that some difference appears already at the level of the sensorimotor synchrony. Our first surprise is that TMS perturbations left the tapping accuracy intact in subjects with schizophrenia, even when profound trajectory deviations occurred.

Our second observation is that the perturbations at the level of M1 were able to induce an alteration in timing perception of schizophrenia patients, and to trigger lapses in the performance of tapping, i.e. higher-level deficiencies related to attention and volition. We believe this provides evidence for the altered connectivity of the schizophrenia network as compared to the normal network. It furthermore suggests the potential use of TMS perturbations as a means to probe connectivity between the components of other distributed networks in the brain of schizophrenia patients.

2. Materials and methods

2.1. Subjects

The experiment was approved by the Shaar Menashe Hospital internal review board. Nine healthy subjects (5 males and 4 females, age 20–48 mean 29.1 ± 8.7, 9 right handed), including two of the authors, and nineteen subjects with schizophrenia (17 males, age 23–47 mean 39.5 ± 5.6, 15 right handed, 2 left handed, and 2 females, ages 27 and 57, both right handed) took part in this experiment, and were paid for their participation. After a complete description of the study was given, written informed consent was obtained.

Patients were diagnosed according to the DSM-IV criteria (First et al., 1995) and rated for symptom severity using the positive and negative symptom scale (PANSS) (Kay et al., 1989). Schizophrenia patients with a history of neurological disorders, comorbidity and drug abuse were excluded from the study. Patient information is given in Table 3, with medication given in equivalent dosage of chlorpromazine. All schizophrenia patients received their regular medication during the time of the experiment. Three patients were on atypical antipsychotic medication in all mean dose equivalent of 412 mg chlorpromazine.

Atypical medication involved therapeutic doses of Ziprasadon, typical medications included Haloperidol, Perphenazine and Fluphnazine. Only two patients, medicated with Perphenazine, needed continuous medications with Biperidon to avoid developing akatisia, and they did not have extrapyramidal symptoms while on medication with Biperidon, thus allowing them to participate in the study. Two patients received Carbamazepine treatment, but at low doses for symptomatic relief only. Patients had, on average, a nine year illness duration with a mixture of positive and negative symptoms prevailing, and were thus diagnosed at times as residual schizophrenia and paranoid schizophrenia depending on aggravated and remission periods. Due to institutional withdrawal, none of the patients used alcohol or other psychoactive drugs during the 3 months before the experiments. Of the 19 subjects with schizophrenia 14 were smokers and 5 were not, while only one of the 9 healthy subjects smoked.

Our study concentrated on phenomena particular to schizophrenia, and therefore included more people with schizophrenia than healthy controls. While some results presented here apply to both groups, of particular interest were the momentary lapses of attention observed abundantly in the majority of the patients tested, but not in the healthy controls. For clarity and for greater statistics, we expanded our study to include more patients, and the size of the control group is discussed in detail below.

2.2. Statistical analysis

The tests that were used to analyze the data in this study were two-sample one-tailed *t*-test for independent

samples, and paired one-tailed *t*-test. When normality was violated Wilcoxon signed rank was used instead of the paired *t*-test. When equality of variance was violated the Satterthwaite *t*-test was used. Spearman correlation, which does not assume normal distributions, was used for all correlation analysis. The analysis of the subjective rating was performed using a 1-way ANOVA with the subjective response as the independent variable (factor) at 4 levels, and the change in accuracy as the dependent variable.

We assessed the necessary size for a statistically significant control group using the statistical notion of power of the experiment. The difference between the healthy controls and the schizophrenia patients is both in the number of lapses observed and in the associated standard deviations. Since the controls have almost zero lapses along with very small standard deviation, the number of subjects needed to obtain statistical significance is smaller. Indeed, the ratio of standard deviations between the control group and the patient group is 1:8.5. This means that the sample size of controls needed to obtain the same significance as for the patient group translates to a ratio of 1:70, while we have a ratio of 1:2 with $N=9$ controls and $N=19$ patients with schizophrenia.

2.3. Design

The design of this experiment was similar to that described in Levit-Binnun et al. (in press). Subjects sat comfortably on a chair with their dominant hand resting on a pad, and tapped with the index finger onto a target marked on the pad, in pace with the beat of metronome clicks at 2.5 Hz transmitted through headphones. A photodiode was fixed into the pad so that the finger allowed light to enter it in proportion to its height above the pad and its position was monitored. Subjects were explicitly asked to tap to the beat as accurately as they could even if perturbations to the finger were produced by the TMS. At the end of each trial subjects were asked to report their subjective judgment about their accuracy and the perturbations they felt by giving a score from '1' to '4'. A score of '1' meant they felt no perturbation at all, '2' that they felt something but it had no interference with the task, '3' that the perturbation interfered with the task but they overcame the perturbation and '4' that they felt that the perturbation was so strong that they could not keep to the beat. Some subjects with schizophrenia found it hard to use the '1'–'4' scale. In this case the exact description of their subjective experience and the experimenter's observation were recorded and translated into the scale of '1'–'4'.

Each experimental session began with a pilot test to determine seven TMS intensities that span the range of the '1'–'4' answers. This was followed by the actual experiment, consisting of 21–35 trials, each including a continuous series of roughly 50 taps. After several taps without TMS (no less than 16), the subsequent 16 taps were performed with the application of TMS. The metronome signal was given for 5 ms at a constant intensity, and one pulse of the TMS was given synchronously with it. The next trial began after subjects reported their subjective experience '1'–'4' (about 20 s). At least 3 trials were performed at each of the seven chosen intensities and the order of the intensities was determined pseudo-randomly to avoid guessing of the next step by the subjects. The pilot tests were not used in the subsequent analysis.

2.4. Measurement of finger motion

The finger position was determined using an efficient yet simple light measurement device based on a photodiode, positioned in the pad on which the finger was tapping. When the finger was resting on the hole it blocked the light from reaching the photodiode and a minimal current was obtained from it. As the finger detached from the pad and moved higher more light entered the hole, and the photodiode current increased. Calibration tests (see Levit-Binnun et al., in press) showed a linear relation between the finger's height and the photodiode's output. This setup allowed measurement of finger trajectory, kinematics, and tapping accuracy simultaneously. We estimated the accuracy in timing to be 5 ms and height accuracy 1 mm.

2.5. TMS parameters

Magnetic stimulation was delivered using a Magstim Rapid (Magstim Company Ltd., Wales, U.K.) magnetic stimulator with a 7 cm figure-of-eight coil. The resting Motor Threshold (rMT), i.e. the minimal TMS energy that elicits at least 5 of 10 50 μV MEP response from the right first dorsal interosseous muscle, was determined using standard procedure (Pascual-Leone et al., 1998). This allowed calibration of the stimulator to the individual brain excitability level and determined the optimal site for activation of the index finger.

The effect of the TMS on the finger was monitored by inspection of the movement displayed online via a dedicated LabView control program and by the subjective rating '1'–'4' given by the subjects (see above). Based on this, a set of seven TMS intensities was chosen for each subject, spanning the range of no

visualized or felt (subjective rating '1') perturbation all the way to a clearly visualized and subjectively rated '4' perturbation. These intensities varied across subjects, distributing around the predetermined rMT. All TMS parameters were in accordance with the recommended safety guidelines (Wassermann, 1998) and never exceeded the range of comfort for the subject.

2.6. Recording and analysis

Light information arriving from the photodiode was digitized and recorded using a National Instruments A/D card (National Instruments Corporation, Austin, TX) together with National Instruments LabView software. The same program was also used to create the metronome clicks, send the triggering signals to the TMS and record the actual TMS stimulation. Data was analyzed using Matlab software (The MathWorks, Inc., Natick, MA). Manual analysis using a special Matlab program was performed to avoid automatic analysis mistakes that arise due to variability in tapping between and within subjects. The points delineating the beginning and end of the periods where the finger was maximally flexed ("down" and touching the pad) and maximally extended ("up" position) and the occurrence of the metronome during the tap cycle were visually identified.

We defined a tap to be "on beat" if the finger was down (maximal flexion) when the metronome occurred. Two healthy subjects were excluded from the analysis. One persistently had their finger in the "up" position when the metronome beat occurred. The other was a professional drummer, and although we expected improved accuracy, his drumming skills seemed to interfere and he was continually off beat. This exclusion is equivalent to a cutoff requiring a minimum tapping accuracy of 30% for healthy subjects. Subjects with schizophrenia, although comparable in their accuracy, were more homogenous in performance and no cutoff was needed.

Most subjects the experiment was repeated more than once (on different days), in total there were $N=20$ and $N=31$ repeats of this experiment for the healthy subjects and subjects with schizophrenia respectively. About 3% and 4% of the total taps, in the case of the healthy subjects and subjects with schizophrenia respectively, were excluded from the analysis because they could not be unambiguously categorized.

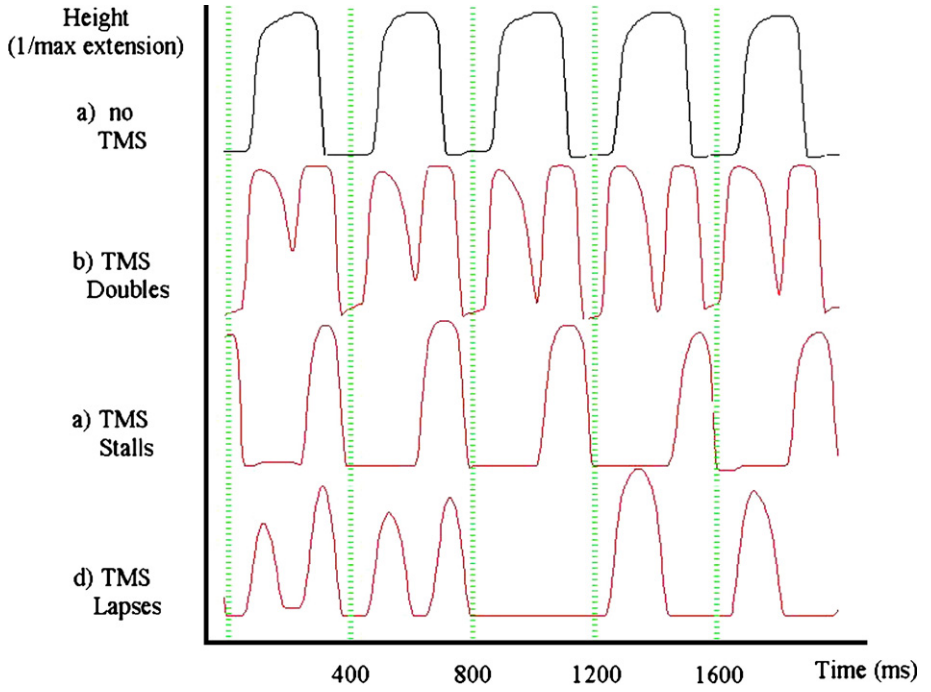

Fig. 1. Finger tapping profiles of subjects with schizophrenia — Measured finger trajectories shown as height versus time. Green dashed lines indicate the time of the metronome click and for b), c), and d) the time of the Transcranial Magnetic Stimulation (TMS) pulse as well. Shown in a) is the typical finger motion without the TMS pulses. b) Shows the doubles wherein an extra flexion is executed halfway between metronome beats. c) Shows the stalls, which include finger inactivity lasting half the time interval of beats. In part d) there is a beat in which no finger motion is observed, preceded by doubles and followed by normal tapping. This effect is particular to subjects with schizophrenia and not to healthy subjects.

3. Results

Fig. 1 shows graphs of the finger height as a function of time during the experiment. Fig. 1a demonstrates the baseline tapping motion of the finger without TMS for subjects with schizophrenia. While the motion is similar in both groups, the subjects with schizophrenia spend ~26% more time at the maximally flexed phase than the healthy subjects ('Down Time' in Table 1). Fig. 1b and c demonstrate the two major effects of TMS perturbations on finger movement in subjects with schizophrenia that were reported recently for healthy subjects as well (Levit-Binnun et al., in press). A "double" is shown in Fig. 1b, and in c a "stall" (Levit-Binnun et al., in press). In the case of a stall, TMS caused the finger to stay at its lowest position for half of the period and then perform a tap in the rest of the period. In a double, TMS caused the finger to perform an extra tapping motion (though not necessarily completing the motion downwards), effectively doubling the frequency of tapping.

A summary of results on tapping with and without TMS is given in Table 1. Subjects with schizophrenia had 46% more stalls than healthy subjects and 28% fewer doubles than healthy subjects (both not statistically significant). As was the case for healthy subjects (Levit-Binnun et al., in press), the distribution of doubles and stalls in the schizophrenia group varied from subject to subject and some were more "stallers" (11 of 19 subjects) while others more "doublers" (7 of 19 subjects), and one patient executed stalls and doubles equally. Table 1 gives the duration of stalling before resuming a tap ("Stall time"), and of the first and second taps in a double ("Double time"). Note that for both groups, both stalls and doubles divide the metronome period in half.

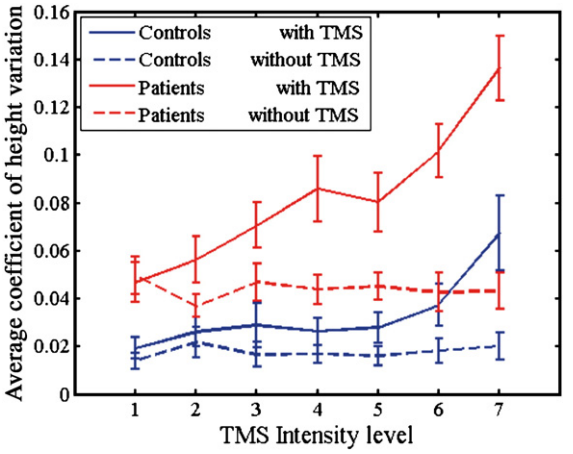

Fig. 2. Height of finger variation for healthy subjects and subjects with schizophrenia — Coefficient of variation (SD/mean) in the maximum height of the finger, plotted versus Transcranial Magnetic Stimulation (TMS) intensity. Red curves are data from subjects with schizophrenia and blue are from healthy subjects. Dashed curves show data from finger tapping without TMS, while solid curves indicate finger tapping with TMS pulses. Subjects with schizophrenia evidently displayed greater deviations in trajectory than healthy subjects. Without TMS these deviations were roughly constant (dashed curves), but were greater with TMS (solid curves), and showed a clear dependence on the magnitude of the applied magnetic field (TMS intensity). Furthermore, the deviation in subjects with schizophrenia follows the same dependence on intensity as in healthy subjects, with an initial increase followed by a constant plateau, with greater deviation at the highest intensities.

Table 1
Summary of finger tapping characteristics: average percentages and times

	Healthy subjects (N=7)	Schizophrenia patients (N=19)
Percentage of stalls (%)	11.2±2.1	16.3±3.7
Percentage of doubles (%)	17.3±3.6	12.4±2.5
Down time (ms)	106±9	134±7
Stall time (ms)	199±45	193±13
Double time 1 (ms)	217±32	210±4
Double time 2 (ms)	184±32	189±4
Tapping accuracy (%)	No TMS 66.3±16.2 TMS 72.0±9.3	No TMS 61.4±19.3 TMS 63.7±24

Average percentage is given for stalls and doubles out of all taps performed with TMS. 'Down time' refers to the duration the finger stayed on the pad when tapping without TMS. 'Stall time' is the duration the finger stayed down during a stall. 'Double time 1' is the time from a metronome click to the nadir of the first flexion in a double, and 'double time 2' is the time from the nadir to the next metronome click. Tapping accuracy is the average percentage of taps in which the metronome occurred while the finger was on the pad (see Materials and methods). Tapping accuracy is displayed for taps without TMS ('no TMS') and for taps with TMS ('TMS'). All values are presented as 'mean'±'standard deviation'.

The major observation made in Levit-Binnun et al. (in press) was that TMS perturbations in healthy subjects did not result in a greater difficulty to stay synchronized with the metronome. In fact, a slight increase in accuracy was seen (Doumas et al., 2005) for the lowest TMS intensities (Levit-Binnun et al., in press). Previous studies led us to expect that schizophrenia patients would be less accurate in tapping even without TMS (Manschreck et al., 1981, 1985) and that TMS perturbations would affect their accuracy (either increasing or reducing it) in a greater manner. Among these are the hypotheses regarding timing deficits in schizophrenia (Davalos et al., 2003; Elvevag et al., 2003) together with reports of motor deficits (Vrtunski et al., 1989; Wolff and O'Driscoll, 1999; Doumas et al.,

2005), and side-effects of medication (Leucht et al., 1999; Tandon and Wolfgang Fleischhacker, 2005).

However, when analyzing across all intensities we found that the probability for controls and patients to be down with the metronome was the same when tapping with TMS and without TMS, and no statistically significant difference was found between the two conditions (see Table 1, "Tapping accuracy"). While for healthy subjects we observed a significant improvement in accuracy at the lower intensities (Levit-Binnun et al., in press), no such increase was observed for the subjects with schizophrenia (data not shown).

TMS had two further effects on the finger motion of people with schizophrenia that were more pronounced than in healthy subjects. Large deviations were seen in the height that the finger achieved in each tap. The distribution of these heights was more irregular for the subjects with schizophrenia than for the healthy subjects. This is shown in Fig. 2, which displays the coefficient of variation (CV) of this distribution as a function of TMS intensity for healthy people and people with schizophrenia. CV is defined as the ratio of the standard deviation of the distribution to its mean, and is a measure of amplitude variation. While the amplitude was more variable in patients even during unperturbed tapping, the application of TMS caused a larger increase in variability for people with schizophrenia, and this increase was even larger at the higher intensities (the increase was significant for intensity levels 2 and 4–7, $P<0.03$, $DF=48$).

The ratio of the up velocity (velocity during extension) to the down velocity (velocity during flexion) is a measure of the asymmetry of the tapping movement. This ratio will be closer to one for more symmetric tapping profiles. Without TMS, the tapping profile of healthy subjects tends to be asymmetric, with a slow up movement and a faster movement toward the target (Balasubramaniam et al., 2004) (average ratio 0.59±0.01). The tapping profile of subjects with schizophrenia, on the other hand, is more symmetric (average ratio 0.66±0.01) and this difference is significant (pooled t-test, $P=0.008$, $DF=49$). Application of TMS perturbations causes a significant increase in symmetry for both groups (for healthy subjects the average ratio is 0.74±0.02, $P=0.0008$, for subjects with schizophrenia the average ratio is 0.87±0.02, $P<0.0001$); this increase is significantly more pronounced for the subjects with schizophrenia (pooled t-test, $P=0.05$, $DF=49$).

Similar to healthy subjects (Levit-Binnun et al., in press), the subjects with schizophrenia were not aware of the abnormal movement of their finger. They only reported a feeling of "losing control" or of the finger "feeling tired".

In order to measure the ability of both healthy subjects and schizophrenia patients to accurately assess their accuracy we calculated the *actual* change in accuracy between tapping without TMS and tapping with TMS for each trial, and compared it to the subjective rating '1'–'4' (see Materials and methods) given for this trial. Accuracy was defined as the number of taps the finger was on beat divided by the total number of taps. Defining A_T to be the accuracy with TMS, A_{nT} without TMS, the change in accuracy is given by $100\cdot(A_T-A_{nT})/A_{nT}$. This normalization of the tapping accuracy during TMS by the tapping accuracy during no TMS was essential, in order to account for trials where tapping accuracy was relatively low even without TMS perturbations.

Table 2 shows what the mean change in accuracy actually was for the different subjective ratings '1'–'4'.

Table 2
Self-judgment of TMS interference for healthy subjects and schizophrenia patients

	Rating '1' (%)	Rating '2' (%)	Rating '3' (%)	Rating '4' (%)
Healthy controls ($N=7$) all intensities	(64±21)	(94±24)	(43±15)	(1±17)
Schizophrenia Patients ($N=19$) all intensities	(66±22)	(24±17)	(23±32)	(26±28)
Patients lowest intensity	(86±30)	(7±11)	(10±8)	

The four columns represent the subjective ratings given on a scale of '1' through '4', with '1' indicating no feeling of TMS and '4' a complete loss of finger control (see Materials and methods for complete description). Displayed are the average changes in tapping accuracy (average±standard error) caused by TMS, for each subjective assessment of the TMS perturbation. Defining A_T to be the accuracy with TMS, A_{nT} without TMS, the change in accuracy is given by $100\cdot(A_T-A_{nT})/A_{nT}$. The first two rows display the average changes in tapping accuracy for all trials and all intensities. A clear decrease in accuracy is apparent for healthy subjects (first row) when they feel greater TMS interference, indicating a general awareness of the TMS effect, though they were unaware of executing doubles or stalls. As they report stronger TMS interference, their taping accuracy decreases. This contrasts with the experience of schizophrenia patients (second row); after an initial drop, the accuracy remains roughly the same, even though the patients are reporting greater TMS interference. Patients of schizophrenia seem to have a cruder sense of perception; they can clearly differentiate a TMS sensation from no TMS, but evidently misjudge the strength of TMS. Patients reported greater interference when actually there was no difference in their accuracy. The third row displays the change in accuracy as measured at the lowest TMS intensity, for schizophrenia patients only. At this lowest intensity, where the effect of TMS was very low (the probability for a '2' or '3' was <20%, and no '4's were reported), schizophrenia patients did respond more faithfully to their actual tapping accuracy. This serves as a control to differentiate between judgment impairment as a result of the TMS versus the effect of the pathology itself.

Table 3
Subject profiles and their rates of lapsing

	Gender	Age	Years of education	Years of illness	Medication: chlorpromazine equivalent dose (g)	PANSS			Percentage of trials with lapses
						Positive mean	Negative mean	General mean	
Patients (N=19)									
IY	M	39	12	10	0.6	3.6	5.6	3.1	21
OY	M	47	12	9	0.6	3.0	6.4	3.5	17
VP	M	38	12	12	0.2	2.9	4.7	2.5	24
HI	M	43	12	13	0.1	4	4.7	3.1	29
OA	M	31	12	9	1.0	3.3	5.1	2.6	10
MK	M	31	12	5	0.2–0.3	4	4.9	2.8	14
SH	M	44	9	12	0.2–0.4	5	6.4	3.5	19
BC	F	57	12	6	0.2–0.4	2.9	6.3	2.9	4
BA	F	27	12	4	0.6	3.1	4.9	2.5	5
AK	M	27	10	6	0.1	4.7	3.4	2.9	5
RK	M	23	9	10	0.2	3.7	3.8	3.0	5
CR	M	37	10	9	0.2–0.3	2.3	5.3	2.6	0
OS	M	40	12	12	0.1–0.2	2.6	4.6	2.2	0
SG	M	28	12	6	0.3–1.0	2.7	5.6	3.3	0
BM	M	45	12	11	0.3–1.0	2.4	4.9	3.1	0
AR	M	38	7	13	0.1–0.2	3.6	5.2	3.0	0
ZA	M	23	12	9	0.2	4.4	5.1	2.9	0
AA	M	28	12	11	0.2	3.0	5.1	2.8	0
SZ	M	34	8	12	0.2	3.9	5.1	2.4	5
Controls (N=9)									
OG	F	23	13						2
JS	M	35	22						0
BH	M	24	14						0
NR	F	23	14						2
MF	F	20	13						0
NH	M	35	24						0
DK	M	30	10						0
IH	F	23	13						0
EM	M	49	21						4

Subjects' initials are given in the leftmost column, and the percentage of trials in which a lapse occurred is given in the rightmost column. While the average age for the control group is 10 years less than the patient group, no correlation exists between lapsing and age (see Results). Medication is listed in terms of equivalent dosage of chlorpromazine. A correlation was found between lapsing and positive PANS scores (see Results). The last two healthy subjects (DK and IH) were excluded from the analysis of accuracy, but their lapsing information is nonetheless given for completeness. The first seven subjects with schizophrenia showed the strongest propensity to lapse, and are termed 'strongly lapsing' in the text.

The first two rows show this relation for all trials at all intensities for the healthy and schizophrenia subjects respectively. A 1-way ANOVA analysis with the subjective rating as factor produced a significant effect for subjective response only for healthy subjects ($P=0.01$, $DF=3$) and not for the subjects with schizophrenia ($P=0.7$, $DF=3$). We attribute the fact that healthy subjects rated '2' rather than '1' when they were (on average) more accurate, to the slight increase in tapping accuracy at low TMS intensities observed by us previously (see Levit-Binnun et al., in press).

The subjective ratings '2'–'4' relate to cases where the TMS perturbations were actually felt by the subjects (see Materials and methods). We thus correlated these three scores with the change in accuracy associated with them (see Table 2, first row, columns 2–4) and found a high negative correlation of −0.99 for the healthy subjects, indicating their high ability to judge the effect of the TMS perturbations on their accuracy (producing the expected negative slope). In contrast, no correlation (0.36) between accuracy and subjective rating '2'–'4' was found for the schizophrenia patients (Table 2, second row, columns 2–4), suggesting a reduced ability in judging the effect of TMS on their accuracy.

It is possible that reduced judgment of accuracy could be a general deficit in schizophrenia and not a consequence of the TMS perturbations. We therefore checked the judgment of accuracy of the patients at the lowest intensity, where TMS perturbations are considered negligible. In this case the distribution of '1's in patient's reports was ~80%

while the distribution of '2's and '3's was ~10–20%, and no '4's were reported. This indicated that indeed patients felt little or no disturbance from TMS at the lowest intensity and that this intensity can serve to control for the effect of the schizophrenia pathology itself on subjective judgment. The last row in Table 2 displays schizophrenia patients' actual change in tapping accuracy versus their subjective rating at the lowest intensity. When significant change in accuracy occurred patients reported '1', while when almost no change occurred they reported '2' and '3'. Thus, with weak TMS perturbations, schizophrenia patients had no problem in judgment of accuracy. The implication is that the impaired ability to judge tapping accuracy at the higher intensities (see second row in Table 2) is not inherent to the schizophrenia pathology, but rather is an effect of the TMS perturbation to M1.

In addition to the doubling and stalling (observed for all subjects with schizophrenia), a subset of patients showed an additional effect of lapsing (Fig. 1d). Lapses are defined as little or no movement of the finger during a full metronome period, occurring at least once during a trial while subjects were tapping with the TMS. In all, lapses occurred in 12 of the 19 patients, and most severely in 7 patients, whom we term strongly lapsing. Lapses occurred with a probability of 9.5–29% in these 7 patients during TMS, while in healthy controls we observed lapses in just 3 subjects, occurring with probability of less than 2–3.6%. The full list of lapse percentages for all participants in our study is given in Table 3, which also includes details on both control subjects and those with schizophrenia.

With the number of subjects we have tested we are able to obtain strong significance for our results. First is the statement that healthy people do not lapse, which is statistically significant ($P=0.04$), with the number of lapses zero within a 3% "background" error given $N=9$ controls and the measured standard deviation. Second, for the question of whether people with schizophrenia do lapse, the answer is yes, which is highly significant ($P<0.003$) for $N=19$. Our ability to determine the average value of lapsing precisely depends strongly on the standard deviation, and our statistical power is 100% for showing that an average value on the order of 10% is different than zero. If we further focus on the "strongly lapsing" subgroup, the statistical power allows even stronger statements regarding the average lapse numbers. For this subgroup the average percent of trials with lapses is on the order of 20%, and the experiment has statistical power of 100% for identifying values in the range of ±10% around this average.

Although there was some difference in the mean age of the two groups of subjects (control group: 29±9, patient group: 39±5), it has no bearing on the lapses. Whether or not a patient will lapse is not correlated with age (0.1, $P=0.24$). However, when correlating the occurrence of lapses for the strongly lapsing with the PANSS (Positive and Negative Symptoms Scale) score of each subject we found a correlation of 0.55 (Spearman correlation, $P=0.04$) with the average score of positive symptoms. No significant correlation was found with the average score of negative symptoms or with the average score of general symptoms. Spearman correlation analysis was also preformed with each PANSS symptom separately. Significant correlation or nearly significant correlation was found between the occurrence of lapses and Delusions (0.68, $P=0.007$), Hallucinatory Behavior (0.58, $P=0.03$), Poor Rapport (0.47, $P=0.09$), and Unusual Thought Content (0.6, $P=0.02$). Lapses were also found to be correlated with the occurrence of stalls (0.63, $P=0.04$) and anti-correlated with the occurrence of doubles (-0.56, $P=0.07$).

All our schizophrenia patients were medicated, some taking typical antipsychotic medication known to have motor side effects (Leucht et al., 1999; Tandon and Wolfgang Fleischhacker, 2005). We found that atypical medication was correlated to the occurrence of stalls (0.58, $P=0.03$), but there was no correlation between the type of drugs (typical or atypical), with the occurrence doubles. Lapsing was also not significantly correlated with medication. Moreover, our results regarding the motor abnormalities and the timing effects were robust, whereas our schizophrenia patient population was heterogonous with respect to the types of medication they were taking. Taken together with past results which showed that there is no significant difference between medicated and non-medicated patients when subjects were asked to tap as fast as they could (Flyckt et al., 1999), we believe that the major effects of TMS perturbations in this study are not related to medication.

Fourteen of the nineteen schizophrenia patients tested in this experiment were heavy smokers (more than a pack of cigarettes per day). We did not find a correlation between being (or not being) a smoker and having (or not having) doubles, stalls or lapses.

4. Discussion

In comparison to healthy subjects, TMS perturbations caused greater responses and variability in the finger movements of subjects with schizophrenia, especially at the high intensities, but they did not elicit a new pattern of tapping. The enhanced sensitivity and severity of motor

anomalies in schizophrenia patients is not very surprising (Vrtunski et al., 1989; Hoy et al., 2004) and is usually attributed to deficits in motor cortical inhibition (Pascual-Leone et al., 2002) and to dysfunction of the dopamine system (Yang et al., 2003, 2004). It is noteworthy that no correlation with dopamine related medication was found. We therefore believe that the differences in motor function between healthy subjects and subjects with schizophrenia can be attributed to such deficiencies, e.g. in the abundance of dopamine receptors or to local deficits in the level of inhibition and excitation of the motor circuit. In contrast to our expectations, TMS perturbations did not affect the timing component, and subjects with schizophrenia were as good as healthy subjects in keeping pace with the metronome.

On the other hand, perturbations applied to M1 did affect the higher brain function related to the judgment of one's own timing, indicating that this higher level component may be tampered with via its interaction with other components in the network. Since this does not occur in healthy subjects, we can conclude that the connectivity of the network is in some way deficient and that the connections are more sensitive to perturbations than in the healthy brain. Abnormalities in the connections between components associated with subjective timing judgment and the other components in the brain relate to previous reports of timing deficiencies (Davalos et al., 2003; Elvevag et al., 2003) and support the "Cognitive Dysmetria" model (Andreasen et al., 1999). They also relate to models suggesting impairment in the mechanism underlying the awareness to an action and the ability to compare its outcome with the intended internal motor plan (Frith et al., 2000; Alain et al., 2002).

We find the occurrence of lapses in patients during TMS perturbations of M1 to be particularly fascinating. Lapses in cognition are known to occur in schizophrenia patients during speech, for example in an interview or during a discussion. A-priori this would seem to be an unrelated, high level deficiency.

Recently, Weissman et al. (2006) described the neural correlates of momentary lapses in attention resulting in increased reaction times to visual stimuli. They provided a system-wide description of this phenomenon, showing how lapses in attention correlated with reduced activation in right frontal areas implicated with control of attention, reduced deactivation of a widespread 'default-mode' network, reduced stimulus-triggered activity in sensory cortices and increased activity in frontal and parietal brain regions involved in the recovery from these lapses (Weissman et al., 2006). The lapses we observe may therefore be associated to the lapses in attention described by Weissman et al. (2006), may originate in similar brain regions, and have similar effects on brain activity, i.e. reduction of processing resources of the behaviorally related areas.

Interestingly, we found correlations between the appearance of lapses and three positive symptoms which all fall within the subgroup of symptoms associated with the "Reality distortion" syndrome of schizophrenia, as defined by Peter Liddle (Liddle et al., 1992). This lends strength to the clinical sub-classification of syndromes suggested by Liddle, and may in the future suggest ways for diagnosis based on generalized forms of lapsing.

The lapsing is very reminiscent of the clinically observed "blocking" phenomenon, where patients momentarily lose the thread of conversation during an interview or discussion. Since we understand the lapsing phenomenon as arising from a transient attentional deficit, we suggest investigating in more depth the phenomenon of blocking, which has not been studied in full to date. We furthermore conjecture that blocking may also be related to the "Reality distortion" syndrome of schizophrenia. Since blocking is clinically difficult to identify, the TMS experiment could serve as an alternative and reliable method for invoking and studying attentional lapses.

One possible explanation for the appearance of lapsing in patients with schizophrenia is the existence of an inherent weakness or instability in the regions responsible for attention (Lewis and Gonzalez-Burgos, 2006). Such a weakness would also explain the "blocking" in patients, where they seem to lose attention momentarily during an interview. Perturbations to M1, similar to internal disturbances in the patient (hallucinations etc.) could perturb the centers of attention sufficiently to cause a lapse. This explanation, however, does not address the fact that lapsing occurs during one or two precise metronome periods.

A potentially more interesting hypothesis is that intervention in one part of the network causes action in another part, but only in patients of schizophrenia. Using the system-wide observation of Friston (1998), Peled (1999), and Weissman et al. (2006), we can frame an explanation for the appearance of lapses that relies on the dysconnection hypothesis (Friston, 1998; Andreasen et al., 1999). We attribute the lapses to the existence of mal-connectivity in the cortical circuitry that regulates the motor control, timing, attention and volition involved in finger tapping. Components of this network should include the prefrontal cortex (Callicott et al., 2003), the anterior cingulate cortex (Paus, 2001), the auditory cortex, the primary and pre-motor cortices (Lewis et al., 2004), the cerebellum (Ivry et al., 2002), the basal ganglia and the sensorimotor cortex (Praamstra

et al., 2003). If we model this network as a block diagram with nodes and links, we can view the occurrence of lapses as evidence of an anomalous effective over-connectivity in the neural circuitry, which is specific to people with schizophrenia. Lapsing in response to TMS indicates that a link exists, through which an excitation created in a low level area such as M1 can impact on higher, cognitive areas, perhaps the ACC or other areas implicated in the appearance of lapses (Weissman et al., 2006). The connection may not be a direct link, and may be relayed through a number of other nodes, but it is not made in the healthy brain. This effective or idealized link may actually be strengthened in reality only by weakening of other, inhibitory links.

The coincidence of motor deficits with the cognitive dysfunction is well known on a clinical basis but is not explained on a theoretical basis. Our work brings together the motor and cognitive aspects and links them conceptually, by showing that perturbations at M1 affect attention in schizophrenia but not in healthy subjects.

While subjects with schizophrenia exhibit similar effects of TMS as healthy controls, in general they were more easily perturbed, and to a greater extent. The lapses, however, are much more specific to schizophrenia. We postulate that the motor cortex is erroneously connected to a cognitive node in the network, by a link that is deficient in people with schizophrenia, a link that may be mediated by other components regulating attention and working memory (Weissman et al., 2006). This suggests that TMS perturbations can be used to alter and possibly to modify connectivity in distributed components of a network (Haraldsson et al., 2004). Ongoing work to determine the nature of these connections, as well as the components involved and methods of correction, holds the promise to demonstrate the utility of TMS in understanding and treating schizophrenia.

5. Contributors

Nava Levit-Binnun: This author designed the experiment, performed the experiment, analyzed data, and wrote the manuscript.

Nestor Z. Handzy: This author designed the experiment, performed the experiment, analyzed data, and wrote the manuscript.

Avi Peled: This author designed the experiment, performed the experiment, and contributed to the writing of the manuscript.

Ilan Modai: This author designed the experiment.

Elisha Moses: This author designed the experiment, performed the experiment, analyzed data, and wrote the manuscript.

Acknowledgments

Work was supported in part by the Clore Center for Biological Physics and the Minerva Foundation, Munich. NZH was supported by the Cuwyn-Lowy Fellowship.

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