Feasibility of single and combined with other treatments using transcranial direct current stimulation for chronic stroke: A pilot study

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Abstract
Objectives: This pilot study aimed to investigate the safety and efficacy of transcranial direct current stimulation (tDCS) for chronic stroke in adult and pediatric patients. We also aimed to verify the efficacy of botulinum toxin A and peripheral neuromuscular electrical stimulation combined therapy involving bilateral tDCS in adult patients with chronic stroke.
Methods: We conducted a pilot study applying an unblinded, non-randomized design. Eleven patients were recruited, and classified into three groups. Group I-a involved bilateral transcranial direct current stimulation and intensive occupational therapy for chronic stroke in adult patients. Group I-b involved bilateral tDCS and intensive occupational therapy for chronic stroke in pediatric patients. Group II involved bilateral tDCS, peripheral neuromuscular electrical stimulation, and intensive occupational therapy after botulinum toxin A injection for chronic stroke in adult patients. Clinical evaluations to assess motor function and spasticity were performed at baseline as well as in 2-week and 4-month follow-up visits. The questionnaire included questions regarding the presence of tDCS side effects, such as headache, redness, pain, itching, and fever.
Results: There were clinically meaningful changes in total Fugl–Meyer Assessment Upper Extremity (FMA-UE) scores at the 2-week follow-up and in the Action Research Arm Test (ARAT) scores at 4-month follow-up in Group I-b. In addition, Group II showed significant improvement in total FMA-UE scores in the 2-week follow-up (p < 0.05) but not on the ARAT scores (p > 0.05). However, Group II showed improvements in total Motor Activity Log scores at both follow-up visits (p < 0.05). No serious adverse events were reported.
Conclusion: The results of this study indicate that tDCS therapy is a potential treatment in pediatric patients with chronic stroke. Furthermore, our data indicate that botulinum toxin A and peripheral neuromuscular electrical stimulation combined therapy may enhance the efficacy of tDCS on motor function.

Keywords
Transcranial direct current stimulation, rehabilitation, stroke, upper limb

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Introduction
Previous longitudinal studies have reported that between 30% and 66% of patients experience upper limb paralysis 6 months after suffering from a stroke.¹⁻³ Recent studies have demonstrated the efficacy of various treatments for patients with chronic stroke, who experience upper limb paralysis, including botulinum toxin A (BTX-A) treatment, functional electrical stimulation therapy, and robotic therapy for functional motor recovery.⁴⁻⁶ In addition, repetitive transcranial magnetic stimulation and transcranial direct current stimulation (tDCS), have been reported to induce...
long-term effects on cortical excitability, lasting for months after the intervention.7,8

tDCS modulates cortical excitability which influences neural plasticity.7 Anodal tDCS (anodal electrode placed
over standard scalp coordinates for motor ipsilesional M1, the cathodal electrode over the contralesional supraorbital
ridge) also modulates cortical excitability in motor areas within affected hemisphere.9,10 Furthermore, bilateral
tDCS, which stimulates both hemispheres simultaneously, could affect excitatory and inhibitory synaptic transmis-
sion in the bilateral motor cortex in patients with chronic stroke.9,11–13 By modulating cortical excitability, tDCS may
alter maladaptive neural plasticity after stroke.9 Moreover, peripheral neuromuscular electrical stimulation (PNMES)
enhances the effects of tDCS on cortical excitability, relative to tDCS alone.14,15 Furthermore, rehabilitation ther-
apy using PNMES combined with BTX-A has been shown to be an effective treatment in chronic stroke or spinal
cord injury.16

However, no studies have examined the efficacy of the use of bilateral tDCS with PNMES and BTX-A therapy
in patients with stroke and upper limb paralysis. Therefore, based on the results of each combination therapy effect
from previous studies, we predicted that a new multiple combination of adding BTX-A to existing tDCS and PNMES
combination therapy would result in more effective results. In addition, tDCS may help improve upper limb paralysis
in pediatric patients with chronic stroke. Since tDCS alone has been rarely used in pediatrics, our pilot study aimed
to investigate the safety and efficacy of tDCS in adult and pediatric patients with chronic stroke. We also aimed
to verify the efficacy of BTX-A and PNMES combined therapy involving bilateral tDCS in adult patients with
chronic stroke.

Methods

Study design

We conducted a pilot study applying an unblinded, non-
randomized design. This study included patients with chronic stroke (>6 months from stroke onset) experiencing paralysis
in an upper limb. Patients between 6 and 85 years old were included. We also excluded patients with epilepsy, complete
paralysis, and/or severe pain, as well as those who were un-
able to follow directions due to cognitive impairment and/or
aphasia. All participants provided written informed consent.
Our institutional review board approved the study. Patient
characteristics are summarized in Table 1.

We included 11 patients (four males and seven females; mean age 43.5 ± 5.1 years) including 7 cases of hemor-
rhagic stroke and 4 cases of ischemic stroke. All study
participants were right handed. There were six cases of right upper limb paralysis and five cases of left upper limb paralysis.
All of four ischemic stroke cases had a lesion in the middle cerebral arterial territory, and three hemorrhagic
stroke patients had a lesion in the putamen, two stroke patients had a lesion in the subcortical, and other two patients had lesions were in the thalamus and pontine. These treatment programs were initiated on 54.9 ± 23.2 days from
stroke onset. Of the included cases, data from 1 patient
(Case 1) was published previously.13

Five patients, included in Group I, underwent bilateral
tDCS therapy alongside intensive occupational therapy
(OT) (Group I-a: two adults; Group I-b: three children). Group II included six adult patients in chronic stroke who
underwent BTX-A and PNMES combined therapy involving bilateral tDCS.

Each rehabilitation session lasted 60 min. Sessions
were performed twice daily for 10 days so that all patients
completed 20 sessions for the 2-week intervention period
in the hospital. In Group I, tDCS started at the same
time as the intensive OT for 25 min; and a 45-min only intensive OT was performed after the tDCS. In Group II, patients
were given a BTX-A injection. Following this, patients
simultaneously underwent intensive OT for 25 min using
tDCS, and PNMES (25 min). Meanwhile, intensive OT
was continued as well, and finally alone intensive OT (10
minutes) was performed (Figure 1). Intensive OT involved
task-oriented training. The content of the task-oriented
training mainly consisted of the task on the desk. The diff-
culty of the task was adjusted for each patient depending
on the extent of their upper limb paralysis and their reha-
bilitation goals. Examples of activities included gripping
or picking up blocks or pegs, varying in size; as well as
using a keyboard and playing cards. The activities
performed by each patient were recorded. In addition,
patients were instructed to increase their use of upper
limb paralysis. After the 2-week intervention period,
patients presented as outpatients and were given exercises
to complete at home. Patients were encouraged to use
their paralyzed upper limbs depending on their individual
rehabilitation needs. Daily activities involved tasks rela-
ted to their own rehabilitation goals from the activities of
daily living (ADL) and instrumental activities of daily liv-
ing (IADL) tasks.

Clinical evaluations were performed at baseline and in
2-week and 4-month follow-up visits conducted after the
intervention. We used the following clinical outcome mea-
sures to evaluate upper limb function, including the Fugl-
Meyer Assessment Upper Extremity (FMA-UE; range: 0–66)
and the Action Research Arm Test (ARAT; range: 0–57).17,18
Limb functioning used during daily activities were assessed
using the Motor Activity Log (MAL; range: 0–5).19
The severity of spasticity symptoms were evaluated using the Disability Assessment Scale (DAS; range: 0–12). DAS evaluations were conducted with patients who had received BTX-A injections. The questionnaire included questions regarding the presence of tDCS side effects, such as headache, redness, pain, itching, and fever.

The effective change in this pilot study was defined as the minimal clinically important difference (MCID) for endpoints with established values, and the MCID for FMA-UE, ARAT and MAL were 4.25, 5.7 and 0.5 points, respectively. Furthermore, the statistically significant difference in the amount of change from the baseline within the group and the presence or absence of serious adverse events were used as reference indicators of feasibility.

**Statistical analysis**

Within-group comparisons were conducted to investigate changes in clinical symptoms (FMA-UE, ARAT, and MAL) before and after treatment using the Wilcoxon signed-rank test. All analyses were performed using SPSS, version 21.0 (IBM Corp., Armonk, NY, USA). The significance threshold was set to $p < 0.05$.

**tDSC-supported rehabilitation**

We used the DC-STIMULATOR PLUS system (neuroConn GmbH, Germany) to perform tDCS. The anodal electrode was placed over standard scalp coordinates for the ipsilesional M1; whereas the cathodal electrode was placed over standard scalp coordinates for the contralesional M1 (C3 or C4 points according to the 10–20 system). Bilateral tDCS using electrodes (size of 5×7 cm; 35 cm²) using a constant current intensity of 2.5 mA for 25 min (Figure 2). Our protocol used current densities below 25 mA/cm² which should not induce damage even when high-frequency stimulation is applied for several hours. The tDCS protocol that we used has been described previously (Figure 3).13,25

**PNMES-supported rehabilitation**

We used an electromyography (EMG)-controlled electrical stimulator, which is also known as an integrated volitional control electrical stimulator (IVES) (OG GIKEN Co, Japan). The IVES is a portable, two-channel neuromuscular stimulator that promotes wrist extension, finger extension, and shoulder flexion during coordinated movement. The system consists of two instruments: a setting/input system and a stimulator.26–28
Two self-adhesive surface electrodes were positioned on the extensor digitorum communis muscles in order to detect the myographic activity triggering the electrical pulse in the same muscle. \textsuperscript{28} IVES therapy sessions were conducted twice daily for 10 days. When IVES (power-assist mode) could not pick up voluntary EMG signals, we selected the normal mode. Stimulation was applied at a frequency of 35 Hz at intervals of 50 µs (duty cycle: ON for 4 s, OFF for 4 s). When the IVES lamp turned ON, patients needed to be conscious of their finger extension movements. Stimulation intensity was set to the level where each patient reported mild paresthesia and muscle contractions in the absence of discomfort.

**Results**

**Baseline characteristics**

We included total 11 patients in this study, Group I-a included two patients (two females; mean age: 64.5 ± 9.2 years; mean interval from stroke onset: 24.5 ± 9.2 months), Group I-b included three patients (one male and two females; mean age: 8.3 ± 0.6 years; mean interval from stroke onset: 98.7 ± 6.8 months), Group II included six patients (three males and three females; mean age: 57.8 ± 9.7 years; mean interval from stroke onset: 41.5 ± 48.1 months). The mean baseline total Fugl-Meyer Assessment Upper Extremity (FMA-UE) score in Group I-a was 55.0 ± 4.2, while the mean proximal and distal FMA-UA scores were 36.0 ± 1.4 and 19.0 ± 2.8, respectively. The mean baseline total FMA-UE score in Group I-b was 42.7 ± 11.0, while the mean proximal and distal FMA-UA scores were 34.0 ± 4.6 and 8.7 ± 6.4, respectively. The mean baseline total FMA-UE score in Group II was 37.5 ± 14.2, while the mean proximal and distal FMA-UA scores were 27.7 ± 7.4 and 9.8 ± 7.4, respectively. The mean baseline ARAT scores in Group I-a, Group I-b, and Group II were 26.0 ± 5.7, 21.3 ± 12.1, and 19.3 ± 19.3, respectively.

The mean amount of use (AOU) score in Group II was 0.9 ± 0.7, while the mean quality of movement (QOM) score was 1.0 ± 0.8. The mean baseline DAS score was 3.0 ± 1.3.

**Clinical outcomes**

The mean total FMA-UE scores in Group I-a were 55.5 ± 4.9 and 52.0 ± N/A at the 2-week and 4-month follow-up,
respectively. The mean total FMA-UE scores in Group I-b were 47.0 ± 12.3 and 46.3 ± 12.9 at the 2-week and 4-month follow-up, respectively. The mean total FMA-UE scores in Group II were 39.5 ± 14.9 and 38.0 ± 13.5 at the 2-week and 4-month follow-up, respectively. The mean proximal FMA-UA scores in Group I-a were 36.0 ± 1.4 and 35.0 ± N/A at the 2-week and 4-month follow-up, respectively. The mean proximal FMA-UA scores in Group I-b were 35.3 ± 5.1 and 35.0 ± 5.6 at the 2-week and 4-month follow-up, respectively. The mean proximal FMA-UA scores in Group II were 28.3 ± 7.5 and 28.3 ± 7.5 at the 2-week and 4-month follow-up, respectively. The mean distal FMA-UA scores in Group I-a were 19.5 ± 3.5 and 17.0 ± N/A at the 2-week and 4-month follow-up, respectively. The mean distal FMA-UA scores in Group I-b were 11.7 ± 7.2 and 11.3 ± 7.5 at the 2-week and 4-month follow-up, respectively. The mean distal FMA-UA scores in Group II were 11.2 ± 7.8 and 9.7 ± 7.2 at the 2-week and 4-month follow-up, respectively.

The mean total FMA-UE scores and the proximal FMA-UA scores in Group II significantly improved compared to baseline total FMA-UE scores at the 2-week follow-up (p = 0.041), the proximal FMA-UA scores at the 2-week follow-up (p = 0.046) and at 4-month follow-up (p = 0.046), respectively. Total FMA-UE scores at the 4-month follow-up (p = 0.339), distal FMA-UA scores at the 2-week follow-up (p = 0.063) and the 4-month follow-up (p = 0.713) were unchanged. The mean ARAT scores in Group I-a were 30.5 ± 9.2 and 26.0 ± N/A in the 2-week and the 4-month follow-up, respectively. The mean ARAT scores in Group I-b were 25.3 ± 15.0 and 27.3 ± 14.0 at the 2-week and the 4-month follow-up, respectively. The mean ARAT scores in Group II were 21.7 ± 19.5 and 22.7 ± 20.2 at the 2-week (p = 0.180) and 4-month follow-up (p = 0.138), respectively (Table 2).

There appeared to be meaningful improvements in Group I-b. These data indicate that there were clinically meaningful changes in total FMA-UE scores in the 2 week and in ARAT scores in the 4 month follow-up in Group I-b. Moreover, Group II also showed significant improvement in total FMA-UE scores in the 2-week and proximal FMA-UA in the 2-week and 4-month follow-up. However, when both Group I-a and Group II were combined, no clinically meaningful improvements in motor function were observed.

The mean AOU scores in Group II increased to 1.2 ± 0.8 in the 2 week (p = 0.027) and 1.4 ± 0.7 4 month follow-ups (p = 0.046); whereas the mean QOM scores in Group II increased in the 2-week (1.3 ± 0.7; p = 0.042) and 4-month follow-up (1.6 ± 0.9; p = 0.026). Improvements in total MAL (AOU and QOM) scores in Group II were also observed at each follow-up visit. Most patients exhibited improvements in use of the affected limb following therapy. The mean DAS score in Group II decreased to 2.2 ± 0.4 and 2.4 ± 1.5 in the 2-week and 4-month follow-up, respectively. Thus, improvements in DAS scores (i.e. spasticity levels) were observed at each follow-up visit (Table 3).

Skin redness and mild itchiness were reported by five patients; however, no serious adverse events were noted (e.g. seizure) during tDCS therapy.

Discussion

This pilot study investigated the safety and efficacy of tDCS in adult and pediatric patients with chronic stroke. We also aimed to verify the efficacy of BTX-A and PNMES combined therapy involving bilateral tDCS in adult patients with chronic stroke. Our results demonstrated the feasibility of tDCS in 11 cases, including three pediatric patients. However, functional improvements in the impaired limb were only
Table 2. Upper limb paralysis function.

| Group | Case | FMA-UE | ARAT |
|-------|------|--------|------|
|       |      | Total (0-66) | Proximal (0-42) | Distal (0-42) | Total (0-57) |
|       |      | Pre | Post | 4M | Pre | Post | 4M | Pre | Post | 4M | Pre | Post | 4M | Pre | Post | 4M | Pre | Post | 4M |
| I-a   | 1    | 58  | 59  | N/A | 37  | 37  | N/A | 21  | 22  | N/A | 30  | 37  | N/A |
|       | 2    | 52  | 52  | 52  | 35  | 35  | 35  | 17  | 17  | 17  | 26.0 ± 5.7 |
|       | Mean (±SD) | 55.0 ± 4.2 | 55.5 ± 4.9 | 52.0 ± N/A | 36.0 ± 1.4 | 36.0 ± 1.4 | 35.0 ± N/A | 19.0 ± 2.8 | 19.5 ± 3.5 | 17.0 ± N/A | 26.0 ± 5.7 |
| I-b   | 3    | 39  | 42  | 41  | 33  | 34  | 34  | 6   | 8   | 7   | 17  | 21  | 23  |
|       | 4    | 34  | 38  | 37  | 30  | 31  | 30  | 4   | 7   | 7   | 12  | 13  | 16  |
|       | 5    | 55  | 61  | 61  | 39  | 41  | 41  | 16  | 20  | 20  | 35  | 42  | 43  |
| Mean (±SD) | 42.7 ± 11.0 | 47.0 ± 12.3 | 46.3 ± 12.9 | 34.0 ± 4.6 | 35.3 ± 5.1 | 35.0 ± 5.6 | 8.7 ± 6.4 | 11.7 ± 7.2 | 11.3 ± 7.5 | 21.3 ± 12.1 |
| II    | 6    | 54  | 56  | 56  | 33  | 34  | 34  | 21  | 22  | 22  | 56  | 56  | 57  |
|       | 7    | 30  | 34  | 31  | 26  | 27  | 27  | 4   | 7   | 4   | 11  | 11  | 11  |
|       | 8    | 46  | 47  | 48  | 34  | 34  | 34  | 12  | 13  | 14  | 23  | 27  | 34  |
|       | 9    | 31  | 29  | 24  | 19  | 20  | 20  | 4   | 4   | 4   | 3   | 3   | 6   |
|       | 10   | 22  | 22  | 24  | 19  | 19  | 19  | 3   | 3   | 5   | 7   | 7   | 5   |
|       | 11   | 50  | 54  | 45  | 35  | 36  | 36  | 15  | 18  | 9   | 16  | 26  | 23  |
| Mean (±SD) | 37.5 ± 14.2 | 39.5± ± 14.9 | 38.0 ± 13.5 | 27.7 ± 7.4 | 28.3± ± 7.5 | 28.3± ± 7.5 | 9.8 ± 7.4 | 11.2 ± 7.8 | 9.7 ± 7.2 | 19.3 ± 19.3 | 21.7 ± 19.5 | 22.7 ± 20.2 |

FMA-UE: Fugl–Meyer assessment (FMA) upper extremity, ARAT: Action Research Arm Test.

*p < 0.05 (Wilcoxon signed-rank test).
observed on specific clinical measures for a subset of patients (Group I-b and Group II).

Previous research indicates that an MCID in patients with chronic stroke can be indexed by a change greater than 4.25 points on the FMA-UE or a change greater than 5.7 points on the ARAT scale.21,22 In our cohort, only Group I-b achieved an MCID for the FMA at the 2-week follow-up and Group I-b achieved an MCID for the ARAT in the 4-month follow-up. The MCID for the MAL is greater than 0.5 points.22 The increased use of upper limb paralysis may induce greater changes in neuroplasticity that may be linked to functional recovery. In functional assessments, Group I-b achieved MCID on clinical assessments during follow-up. Similarly, Group II achieved an MCID of 4-month follow-up assessment.

Improvements in total FMA-UE and proximal FMA-UA scores in Group II were observed at the 2-week follow-up. Previous studies have reported that tDCS is effective when administered in combination with other modalities such as upper limb robot therapy and virtual reality therapy,29 suggesting that combined therapy involving tDCS may enhance upper limb function. Therefore, Group II may have had an enhanced effect of treatment.

Several studies have shown that childhood is a time where brain anatomy and connectivity change significantly.30–33 There is also evidence of changes in brain plasticity during childhood.33–37 Since tDCS may promote plasticity,34 children receiving tDCS may have shown improved clinical outcomes due to changes in synaptic plasticity. However, it is not possible to determine whether changes in the 4-month follow-up visit are due to changes in plasticity due to treatment or due to normal neurodevelopment in childhood.

Interestingly, improvements in DAS scores were observed in the 4-month follow-up, even after the effects of BTX-A therapy had faded. Motivation for continuing self-training was important. MAL scores indicated that our rehabilitation program motivated Group II patients to use their affected limb after completing the 2-week treatment program. Previous studies have reported that the recovery of motor function after a stroke depends on the level of use of the affected limb.38 Therefore, the program of Group II may have enhanced the effect of treatment.

Functional interhemispheric imbalances inhibit the recovery of upper limb paralysis.9,39,40 A previous study suggested inhibitory signals from the ipsilesional hemisphere suppressed activity in the contralesional hemisphere in patients with stroke. This abnormal signaling pattern prevented functional motor recovery.41 The two tDCS electrodes were placed symmetrically to address this interhemispheric imbalance. Moreover, our previous functional near-infrared spectroscopy studies have indicated that this procedure suppresses abnormal activity in the ipsilesional hemisphere (Figure 3).13,25

Although our data demonstrate the potential treatment of tDCS therapy either alone or in combination with other therapeutic modalities, there are several important limitations that require consideration. We only included 11 patients, and the sample was further split into pediatric and adult patients. Another limitation of the study was that different protocols for different age were used. In addition, the number of modalities is very large to study the effects of this study Group II. It should also be noted that cortical stimulation using tDCS may have promoted neuroplasticity.41 Moreover, pediatric patients may have experienced spontaneous recovery over time since changes in neuroplasticity are shown in

### Table 3. Use of impaired upper limb and affecting of muscle tone in ADL

| Group | Case | MAL | DAS |
|-------|------|-----|-----|
|       |      | Amount of use (0-5) | Quality of movement (0-5) |
|       |      | Pre | Post | 4M | Pre | Post | 4M | Pre | Post | 4M |
| I-a   | 1    | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
|       | 2    | 1.5 | 2.5 | 2.2 | 2.0 | 2.8 | 2.5 | N/A | N/A | N/A |
| Mean  |      | N/A | N/A | N/A | 2.0 | 2.8 | 2.5 | N/A | N/A | N/A |
| I-b   | 3    | 0.6 | 1.4 | 1.7 | 0.6 | 1.4 | 1.7 | N/A | N/A | N/A |
|       | 4    | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
|       | 5    | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Mean  |      | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| II    | 6    | 0.9 | 1.9 | 2.4 | 1.6 | 2.2 | 2.9 | 4   | 2   | 1   |
|       | 7    | 0.5 | 0.6 | 0.8 | 0.5 | 0.7 | 0.8 | 2   | 2   | 2   |
|       | 8    | 2.0 | 2.2 | 2.2 | 2.1 | 2.1 | 2.3 | 2   | 2   | 2   |
|       | 9    | 1.4 | 1.6 | 1.3 | 1.1 | 1.4 | 1.4 | 3   | N/A | N/A |
|       | 10   | 0.5 | 0.6 | 0.8 | 0.7 | 0.9 | 1.0 | 2   | 2   | 2   |
|       | 11   | 0   | 0.5 | 1.1 | 0   | 0.7 | 0.9 | 5   | 3   | 5   |
| Mean (±SD) | 0.9 ± 0.7 | 1.2* ± 0.8 | 1.4* ± 0.7 | 1.0 ± 0.8 | 1.3* ± 0.7 | 1.6* ± 0.9 | 3.0 ± 1.3 | 2.2 ± 0.4 | 2.4 ± 1.5 |

MAL: Motor Activity Log; AOU: amount of use; QOM: quality of movement; DAS: Disability Assessment Scale.

*<p><0.05 (Wilcoxon signed-rank test).
children. Nonetheless, our results highlight the need for further studies involving a larger number of cases, a control group subjected to sham stimulation (control) and a uniform treatment protocol.

**Conclusion**

The results of this study demonstrate that tDCS therapy is a potential treatment for chronic stroke in pediatric patients. Furthermore, our data indicate that BTX-A and PNMES treatment combined therapy involving tDCS may support the recovery of motor function. Additional, rigorously designed studies are required to verify our findings.

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**Ethical approval**

Ethical approval for this study was obtained from institutional review board (IRB) named “Fukuoka University-Medical Ethics Review Board” (IRB approval number: 15-2-07).

**Informed consent**

Written informed consent was obtained from all subjects for this study. We have obtained written informed consent from the legally authorized representatives of subjects who were either minor or if they did not have the decisional capacity to provide the informed consent.

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