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Dynamics of Changes in the Level of Cognitive Functioning Among Patients After SARS-CoV-2 Infection – A Proposal for Remote Neuropsychological Assessment in a Longitudinal Study[1]

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Abstract

Study purpose: The aim of this longitudinal study was to assess the cognitive functioning of people who had COVID-19, to determine the dynamics of changes observed in this area over a period of 3–4 months, to compare the patients' results with those of a control group, and to verify the usefulness of a new method of remote neuropsychological assessment.

Method: A longitudinal study was conducted using the Brief Test of Adult Cognition by Telephone (BTACT) neuropsychological assessment tool, which was translated into Polish for the purpose of the study. The study included subjects following SARS-CoV-2 infection (COVID(+) group) and control subjects (COVID(–) group). Cognitive functions in both groups were assessed twice, 3–4 months apart. The study was conducted from July 2020 to January 2022.

Results: Data comparisons were performed using mixed ANOVA with repeated measures. Compared to the COVID(–) group, the COVID(+) group scored significantly lower on the first and second measurements of the Backward Digit Span Test and on the first measurement of the Number Series Test. Additionally, an improvement was observed in COVID(+) group scores in the second measurement compared to the first measurement in: Rey Auditory-Verbal Learning Test (RAVLT) in both the immediate and delayed recall condition; the Backward Digit Span Test, the Number Series Test and 30 Seconds and Counting Task (30-SACT).

Conclusions: The obtained results show an impairment in working memory functions and inductive reasoning in COVID(+) subjects compared to COVID(–) subjects. In addition, the study indicates the usefulness of BTACT in tracking the changes in cognitive functioning over time in individuals following SARS-CoV-2 infection. Tests to assess working memory (Rey Auditory-Verbal Learning Test (RAVLT), Backward Digit Span Test) and a test of inductive reasoning (Number Series Test) appear to be particularly useful in monitoring the mentioned changes.

Keywords: COVID-19, long-COVID, cognitive functions, neuropsychological assessment, remote testing methods

During the COVID-19 pandemic, which lasted from March 2020 to May 2023, more than 6 million cases of infection were reported in Poland alone (covid19.who.int).

One of the postulated routes of entry of the SARS-CoV-2 virus into the CNS is through the nasal mucosa, migrating across the ethmoid bone to the olfactory bulb and along the olfactory pathway, vagus or trigeminal nerve into the brain tissue (Boldrini et al., 2021). Virus from the rhinencephalon area can migrate to other areas of the CNS. Histopathological analyses have shown microglia nodules and neuronal phagocytosis primarily in the brainstem region, less frequently in the cortex or limbic system (Yong, 2021). The virus also crosses the blood-brain barrier and impairs its protective effect by apparently inducing multiple inflammations within the endothelial lining of blood vessels, which may lead to microhaemorrhage on the one hand and ischaemia in specific areas of the brain on the other (Lee et al., 2022). Other direct consequences of virus infection

within the nervous system may include – depending on the severity of the infection – encephalitis and/or meningitis, fatigue, various neuropathies, sleep disorders, mood disorders (depression, anxiety), and within cognitive functioning: impaired attention, speed of information processing, memory (especially within correct name updating) or executive functions (Heneka et al., 2020).

However, it appears that the patient's fight against the disease does not end with the end of the infection. A number of disorders are observed among recovered patients, persisting long after the end of the disease. The varied long-term consequences of SARS-CoV-2 infection are referred to as *long-COVID* (Crook et al., 2021).

Impairment of cognitive functions are one of the most common difficulties being reported by the COVID-19 survivors. The impairment affects: memory, attention, executive functions, processing speed (Zhao et al., 2024), various aspects of language functions and are observed both immediately after the end of the infection (Almeria et al., 2020; Helms et al., 2020;) and several weeks after the end of the illness (Malinowska et al., 2022; Moreno-Pérez et al., 2021; Ortelli et al., 2021; Raman et al., 2021; Whiteside et al., 2021). According to some studies, cognitive impairment may be present in approximately 12–17% of patients three months after the onset of the disease (Savarraj et al., 2021; Tomasoni et al., 2021), and according to others, up to 50% of subjects after more than six months (Frontera et al., 2021).

The occurrence of the above deficits may be directly related to structural changes in the brain that according to studies using various neuroimaging techniques may occur in association with COVID-19 (Egbert et al., 2020). Other studies indicate the presence of inflammatory processes that can take place within brain tissue for up to one year after an experienced infection (Michael et al., 2023). Thus, patients' level of functioning will depend on the short- and long-term response of the immune system. It appears that patients receiving corticosteroids during therapy ultimately underwent a milder infection and recovered more quickly and effectively (Klein et al., 2023), and those with long-COVID symptoms had overall lower serum cortisol levels. Some work has also described reduced levels of gonadotropins within the CNS, which, in the long term, may contribute to accelerated aging of brain tissue and a higher risk of the onset of dementia-like disorders (Davis et al., 2023; Rasika et al., 2024).

According to selected reports, cognitive impairment can develop in patients irrespective of the severity of symptoms during the course of the disease, and also affects young individuals, whose disease course qualified as mild (Del Brutto et al., 2021; Woo et al., 2020).

NeuroCovid research group is one of the research teams collecting data on the cognitive functioning of COVID-19 survivors in Poland and it was established at the Faculty of Psychology of the University of Warsaw (UW) under the leadership of Professor Emilia Łojek. The team began its activities back in 2020, when it was no longer possible to assess cognitive functions with traditional neuropsychological tests due to the sanitary regime in place. It became necessary to reach for remote methods such as online surveys and telephone surveys.

Conducting an assessment of cognitive functioning using remote testing methods has some limitations. This form of testing deprives the possibility of fully observing the patient's behaviour and responses (Sozzi et al., 2020), it may

not be suitable for certain clinical populations (e.g. seniors with established hearing loss or advanced dementia; some psychiatric patients) and it poses problems related to maintaining consistent test conditions for all subjects (Parlar et al., 2020). According to Sozzi and colleagues, remote methods should only be used in cases where cognitive functioning assessment cannot be postponed and carried out directly, face-to-face. At the same time, it is worth noting that remote methods also have some advantages, e.g. convenience, flexibility and access to patients, who are not at home (Bloch et al., 2021). Even before the COVID-19 pandemic, Brearly et al. in 2017 conducted a meta-analysis to compare remote and stationary testing methods. According to the results, the form of testing was significant for motor function tests and tests based on visual material, but in verbal tests (e.g. fluency tests, word list learning, number repetition), no significant differences were observed between remote and stationary tests (Brearly et al., 2017). Also, more recent reports from Barcellos and colleagues, 2021, indicate that verbal memory tests and processing speed tests can be effectively performed using remote methods (Barcellos et al., 2021).

For the purpose of the study, NeuroCOVID research group developed a Polish translation of the Brief Test of Adult Cognition by Telephone (BTACT) test battery (Lachman et al., 2014). NeuroCovid team's longitudinal study was not only one of the first practical uses of BTACT in Poland, but it was also one of the first in our country to investigate cognitive functioning in people after SARS-CoV-2 infection using remote testing methods.

The aim of the conducted study was to assess the cognitive functioning of COVID-19 survivors as comprehensively as possible under the given conditions, assessing the dynamics of these changes over a period of approximately 3–4 months and comparing the results obtained by the clinical group with those of the control group.

Methods

The study included two following groups: subjects who tested positive for COVID-19 (experimental group, hereafter COVID(+)) and subjects who, to the best of their knowledge, were not infected with COVID-19 and had never been tested positive (control group, hereafter COVID(–)). At the initial stage of the study, individuals with a positive PCR test result were eligible for the COVID(+) group; in the subsequent course of the outbreak, antigen tests available in pharmacies were also included as an inclusion criterion for the COVID(+) group. Recruitment of study participants was conducted via social media and in collaboration with the study panel among registered panel users. Study participants were informed of the purpose of the study being conducted and gave their voluntary consent to participate. The study was conducted from July 2020 to January 2022.

The results presented in this article regard people who, according to information obtained in another part of the project in question (a self-completed online questionnaire on broadly defined functioning during and after infection or

during the pandemic in general), had no history of cardiovascular disease, neurological disease, oncological disease or history of psychiatric treatment and declared a mild course of illness when infected (according to WHO definition guidelines[4], 2023 or NIH guidelines[5], 2023).

Study Participants

A total of 177 people participated in the two telephone survey: 133 persons classified as COVID(+) and 44 persons classified as COVID(–). The majority of the sample was female (70.6%) with higher education (74.6%). Participants with secondary education accounted for 24.3% of the total study sample, while those with primary education accounted for 1.1%. The age range of the respondents was 18 to 74 years, and the average age was $M = 41.7$.

Analysis by Student's t-test (with a large difference in the size of the groups of subjects) showed no significant difference in the mean age of the subjects in the two conditions analysed $t(175) = 1.90$, $p = .05$. It can be assumed that subjects in the COVID(+) group had on average the same age ($M = 40.56$, $SD = 13.71$) as those in the COVID(–) group ($M = 45.18$, $SD = 14.71$).

Analysis with the Chi² test showed no significant differences in the sex of the subjects between the study groups $\chi^2(1) = 0.48$, $p = .827$.

Analysis with the Chi² test showed no significant differences in the education of the subjects between the study groups $\chi^2(2) = 5.80$, $p = .055$.

Detailed socio-demographic data of the subjects are presented in Table 1 (p. 144).

Research Tools

The study used Brief Test of Adult Cognition by Telephone (BTACT) test battery, which was developed in 2014 by a team from Brandeis University in Massachusetts, including Margie E. Lachman, Stefan Agrigoroaei, Patricia A. Tun and Suzanne L. Weaver. The BTACT provides a cross-sectional assessment of cognitive functions such as verbal episodic memory, working memory, executive functions, processing speed, verbal fluency, reaction time, attention and task switching, inhibitory control and inductive reasoning. The overall testing time using the BTACT is approximately 20 minutes. The test includes detailed instructions for each subtest, which also specifies the range of questions and comments that are admissible during the conducted assessment (Lachman et al., 2014).

[4] WHO (World Health Organisation) definition of mild infection: patients with symptoms meeting the case definition for COVID-19 without features of viral pneumonia or hypoxia.

[5] NIH (National Institute of Health) definition of mild infection: people who have any of the various signs and symptoms of COVID-19 (e.g. fever, cough, sore throat, malaise, headache, myalgia, nausea, vomiting, diarrhoea, loss of taste and smell), but who do not have dyspnoea or abnormal chest imaging.

Table 1

Sociodemographic Variables of the Study Group

Group	Gender	Age (in %)	Education level (in %)
General COVID(+): n = 133 COVID(–): n = 44	F: 133 M: 44	18–74 y.o. M = 41.7	Primary education: 1.1 Secondary education: 24.3 Higher education: 74.6
Experimental group COVID(+): n =133	F: 95 M: 38	18–24 y.o.: 9.8 25–24 y.o.: 29.3 35–44 y.o.: 27.1 45–54 y.o.: 15 55+: 18.8 M = 40.56; SD = 13.71	Primary education: 9.8 Secondary education: 28.6 Higher education: 70.7
Control group COVID(–): n = 44	F: 30 M: 14	18–24 y.o.: 2.3 25–24 y.o.: 27.3 35–44 y.o.: 22.7 45–54 y.o.: 18.2 55+: 29.5% M = 45.18; SD = 14.71	Primary education: 2.3 Secondary education: 11.4 Higher education: 86.4

The BTACT battery is not the only battery of tests that allows remote assessment of cognitive function. There are many similar tools, but they are often only screening tools. Worth mentioning here are: The Telephone Interview for Cognitive Status (TICS), the telephone version of The Mini Mental State Examination (MMSE), the Telephone Montreal Cognitive Assessment, TELE etc. (Carlew et al., 2020). More cross-sectional tools that allow for the assessment of diverse cognitive functions using a non-face-to-face method include the Brief Assessment of Cognition (BAC) (Atkins et al., 2022) and the Cambridge Automated Neuropsychological Test Battery (CANTAB) (Rapp et al., 2012). Both test batteries are computer-based and were developed not only for remote testing, but also provided opportunities for subjects to complete the tests themselves. However, there are limitations to this: the level of test scores obtained may depend on the level of computer literacy (Smith et al., 2013). Another test which, similarly to the BTACT, is conducted by telephone and allows for an in-depth (i.e. non-screening) assessment of cognitive function is the Telephone-Administered Cognitive Test Battery (TACT). A test-retest reliability test comparing results from a telephone-based test and a re-test conducted onsite showed high correlations. However, tests conducted outside the UK and results describing the diagnostic accuracy of the TACT are lacking (Carlew et al., 2020).

The NeuroCovid research team ultimately decided to use the BTACT battery of tests, the utility of which has been confirmed by studies conducted in people of different ages and from diverse populations (Carlew et al., 2020). The use of the telephone method avoids underreporting of results in those who are not

computer literate (so primarily older people). In addition, the telephone call allows at least partial control of the survey conditions (e.g. noise level or presence of third parties during the survey).

The Brief Test of Adult Cognition by Telephone is a test that has never been used in Poland before and has no Polish adaptation. For the purposes of the described study, a Polish experimental version was developed in translation by Anna Egbert and other members of the NeuroCovid team. The test was translated from English into Polish, but no pre-tests for the Polish-language version or tests using back-translation were conducted. Therefore, it was not verified that the Polish-language version was equivalent to the English-language version. Nevertheless, it was decided to use the experimental version of the translation due to the urgent need to assess the cognitive function of patients after COVID-19. The sanitary restrictions in place at the time significantly limited the possibility of conducting adaptation studies for the Polish-language version of the tool. Such restrictions no longer exist today, so the tool should be adapted before using the Polish translation of BTACT in further research.

Four equivalent versions were developed for the original English-language BTACT battery: A, B, C, D, of which versions C and D were translated into Polish (with the permission of the creators of the original versions). Each version consists of the same tasks, carried out in the same order, but based on different numerical and lexical material.

The battery consists of six tests: two original and four derived or constructed from previously available standardised neuropsychological tools. The tests are administered in the same order as described below.

1. Rey Auditory-Verbal Learning Test (RAVLT) is carried out in two conditions: immediately after hearing the verbal material and after delayed – at the end of the whole test (Rey, 1964).
2. The Backward Digit Span was taken from the Wechsler WAIS III Intelligence Scale (Wechsler, 1997).
3. Category Verbal Fluency Test uses lexical categories. Verbal fluency tests are a widely used method, first described in 1967 by Borkowski, Benton and Spreen (Borkowski et al., 1967). In BTACT, the performance time is 1 minute and the number of responses is counted overall and in intervals of 15 seconds. The lexical category used in the C version of the BTACT test was ‘animals’, while in the D version it was ‘names’.
4. Stop and Go Task Switch (SGST) requires the subject to respond correctly verbally (either ‘stop’ or ‘go’) upon hearing the words ‘red’ or ‘green’. The test consists of three separate trials based on different instructions. It is an original test developed for the BTACT and allows the assessment of reaction time, attention and attentional processing skills and inhibition processes (Lachman et al., 2014).
5. The Number Series Test – the subject is asked to listen to a sequence of numbers and notice the relationships between them and then calculate the last number in the sequence. The test was developed along the lines of previously described number sequence tests (Salthouse and Prill, 1987; Schaie, 1996), but uses new, original number material.

6. 30 Seconds and Counting Task (30-SACT) requires the subject to count backwards, starting at 100, subtracting 1 at a time. 30 seconds is allotted for the test – a short original test developed for BTACT to assess processing speed (Lachman et al., 2014).

Psychometric Values of BTACT

The diagnostic accuracy of the individual tests of the BTACT battery was verified by comparing them with the tests included in the Boston Cognitive Assessment (BOCA). Correlations between the tests ranged between .42 and .54 and were statistically significant at the $p < .001$ level (Lachman et al., 2014). The reliability of the test was assessed using the test-retest method in separate tests for parallel versions A and B. Reliability coefficients for the parallel versions ranged from .55 to .94 in the first measurement and between .52 and .85 in the second measurement. The exception was the fluency test, which had a test-retest reliability of .30, which may suggest that there are significant differences in performance on this test depending on the lexical category used in the test (Lachman et al., 2014).

Comparison test was conducted using a battery of BTACT tests over the phone and directly 'face-to-face' to verify whether the testing method influenced the subjects' scores. Statistical analysis showed no significant differences in this regard (Lachman et al., 2014).

Assessment Procedure

The study conducted by the NeuroCovid research group was a longitudinal study, cognitive functions were measured using the BTACT on two occasions, 3–4 months apart. The first and second measurements used different, equivalent versions of the tests: the C and D versions. The measurements were carried out by psychologists from the NeuroCovid research group. Usually, the first and second measurements were carried out by the same person, but in some cases there was a change of specialist carrying out the second measurement. These changes were due to the varying availability of the researchers regarding study dates, which were adapted to the participants. The subjects were asked to indicate a time when they would be able to stay in a quiet and calm place, allowing for optimal concentration of attention. At the beginning of the study, participants were asked about their wellbeing – in case of illness or declared fatigue, the study was postponed and a new date was set. Before the start of the study, participants were informed that the content of the tasks will not be repeated and that they were not allowed to take notes during the study.

Data Analysis

The data collected was analysed in a pooled manner, ensuring the anonymity of the subjects. Conditions were met for the tested variables to allow

data comparisons to be made using multivariate analysis of variance with repeated measures.

Results

The results for comparisons of mean scores for each method between and within groups are presented below.

Rey Auditory-Verbal Learning Test (RAVLT) – Immediate Recall of a List of 15 Words

Participants from the COVID(+) group had significantly higher mean scores ($F(1,175) = 1.090$, $p < .001$) in the second measurement. There was no significant change in mean scores over time in the control group. There were no significant differences in mean scores between the COVID(+) and COVID(–) groups in any of the measurements.

Rey Auditory-Verbal Learning Test (RAVLT) – Delayed Recall of a List of 15 Words

Participants from the COVID(+) group had significantly higher mean scores ($F(1,175) = 9.084$, $p = .003$) in the second measurement. There was no significant change in mean scores over time in the control group. There were no significant differences in mean scores between the COVID(+) and COVID(–) groups in any of the measurements.

Backward Digit Span

Individuals in the COVID(–) group had significantly higher mean scores compared to those in the COVID(+) group in both the first and second measurements ($F(1,174) = 9.832$, $p < .001$). Those in the COVID(+) group had significantly higher mean scores in the second measurement: $F(1,174) = 15.776$, $p < .002$.

Category Verbal Fluency

Participants from the COVID(+) group had higher mean scores over time, but the difference between measurements over time did not prove to be statistically significant. The mean score of those in the COVID(–) group decreased over time, but again the difference between measurements over time did not prove to

be statistically significant. There were no significant differences between the mean scores of subjects in the COVID(+) group and the mean scores of subjects in the COVID(–) group on any of the verbal fluency measures.

Table 2

Comparison of the Mean Test Results Obtained by the COVID(+) Group and the COVID(–) Group in the First and Second Measurements

Test	COVID(+) group	COVID(–) group
Rey Auditory-Verbal Learning Test (RAVLT): immediate recall	First measurement $M = 7.87$; $SD = 0.215$ Second measurement $M = 8.71$; $SD = 0.215$	First measurement $M = 8.55$; $SD = 0.373$ Second measurement $M = 8.89$; $SD = 0.373$
Rey Auditory-Verbal Learning Test (RAV: delayed recall	First measurement $M = 6.2$; $SD = 0.246$ Second measurement $M = 6.94$; $SD = 0.246$	First measurement $M = 6.5$; $SD = 0.428$ Second measurement $M = 7.25$; $SD = 0.428$
The Backward Digit Span (WAIS III)	First measurement $M = 4.22$; $SD = 0.114$ Second measurement $M = 4.58$; $SD = 0.114$	First measurement $M = 5.05$; $SD = 0.197$ Second measurement $M = 5.09$; $SD = 0.197$
Category Verbal Fluency Test	First measurement $M = 26.87$; $SD = 0.686$ Second measurement $M = 27.89$; $SD = 0.686$	First measurement $M = 27.5$; $SD = 1.193$ Second measurement $M = 27.05$; $SD = 1.193$
The Number Series Test	First measurement $M = 2.5$; $SD = 0.107$ Second measurement $M = 2.78$; $SD = 0.107$	First measurement $M = 3.07$; $SD = 0.186$ Second measurement $M = 3.2$; $SD = 0.186$
30 Seconds and Counting Task (30-SACT)	First measurement $M = 69.38$; $SD = 0.431$ Second measurement $M = 68.22$; $SD = 0.431$	First measurement $M = 68.93$; $SD = 0.749$ Second measurement $M = 68.64$; $SD = 0.749$

Number Series Test

Participants from the COVID(–) group had significantly higher mean scores compared to those in the COVID(+) group on the first measurement $F(1,175) = 3.870$, $p = .05$). Those in the COVID(+) group had significantly higher mean scores in the second measurement: $F(1,175) = 7.154$, $p = .008$. There were no significant differences between the groups in the second of the measurements.

30 Seconds and Counting Task (30-SACT)

In the COVID(+) group, significantly higher mean scores were observed on the second measurement compared to the first measurement in the same group:

$F(1,175) = 7.325$, $p = .007$. No significant differences were observed between the scores of the COVID(+) group and the COVID(–) group. The mean scores of the two groups in the 30 Seconds and Counting Task (30-SACT) did not differ significantly between them in either the first or second measurement.

Discussion

It has been recommended, both worldwide and in Europe, to consider conducting remote neuropsychological assessments when face-to-face examinations were not possible for various reasons (e.g. excessive geographical distances) (Brearly et al., 2017).

The limitations due to the COVID-19 pandemic have, in a way, forced the use of remote testing methods in assessing the level of cognitive functioning of people experiencing SARS-Cov-2 infection (Cysique, et al., 2021; Sumpter et al., 2023). Surprisingly, the pandemic appears to have increased the number of remote neuropsychological assessment consultations (video calls on platforms or over the phone), but not the overall number of formal contacts in this regard itself (Webb et al., 2022).

In the work of the NeuroCovid research group based at the Faculty of Psychology at the University of Warsaw, the choice was made for the BTACT series of tests (Lachman et al., 2014). The results obtained in the series of tests suggest the possibility of using the tool in situations where physical contact with the subject is difficult.

The profile of the results obtained allows us to note the usefulness of the tool in neuropsychological assessment, both in relation to changes in longitudinal testing over time within the COVID(+) experimental group (see Results: Rey Auditory-Verbal Learning Test (RAVLT) in the first and second measurements, Backward Digit Span Test in the second measurement, Number Series Test in the second measurement, 30 Seconds and Counting Task (30-SACT)), as well as in the comparison between the COVID(+) experimental group and the COVID(–) control group (see Results: Backward Digit Span, Number Series Test in the first measurement).

The change included a significantly statistically higher mean level of performance within the experimental group on the second measure compared to the first measure, and a significantly lower mean level of performance compared to the control group. Thus, the tool appears to be useful both in tracking the change in cognitive functioning over time within the COVID(+) group and when relating its performance to the COVID(–) group, whose performance remained constant over time.

Certain tests proved to be helpful in assessing changes in the level of functioning of, above all, working memory (Rey Auditory-Verbal Learning Test (RAVLT), Backward Digit Span Test) and inductive reasoning (Number Series Test). At this point, it may be mentioned that the latter task was, in subjective assessment, the most difficult for both experimental and control subjects.

In research, it is useful to control for the level of motivation of the subjects, which may fall, for example, due to being in the control group, especially in subsequent measurements, as in the case of the mean level of the results of the Category Verbal Fluency Test.

As the results of the Stop and Go Task Switch (SGST) did not show differences between or within the groups to any extent, it was decided not to present them. It is likely that in the future, in order to capture the change in the level of inhibitory control and controlling function of attentional processes, digital measurement of reaction time should be considered in this type of task.

The results obtained appear to be consistent with those presented in the literature when using tools such as MoCA or MMSE for the remote assessment of cognitive functioning levels, even before the pandemic (Bianchetti et al., 2019). Other sources point to the possibility of comparing the results obtained in face-to-face neuropsychological assessments, using traditional 'face-to-face' methods, with those using tests using videoconferencing and digital versions of traditional tools (Takakura et al., 2023).

Some studies indicate the persistence of impairments in concentration, attention, memory, executive functions among the following populations of study subjects: women, middle-aged people (35-49 years), people with lower socioeconomic status and people with more difficult access to large diagnostic facilities (Adjaye-Gbewonyo et al., 2022).

Due to the small size of the experimental group, and in particular the control group, and the recruitment of people with a relatively mild course of SARS-CoV-2 infection (according to the WHO definition guidelines, 2023) to the study, it is difficult to generalise the results obtained in the project to the population as a whole, but the study indicates opportunities for further work in the development of remote neuropsychological assessment methods.

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