HHS Public Access
Author manuscript
J Int Neuropsychol Soc. Author manuscript; available in PMC 2022 July 24.

Published in final edited form as:
J Int Neuropsychol Soc. 2022 July ; 28(6): 642–660. doi:10.1017/S1355617721000862.

Assessment of Neurocognitive Functions, Olfaction, Taste, Mental, and Psycho-social Health in COVID-19 in Adults: Recommendations for Harmonization of Research and Implications for Clinical Practice

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[a]Conflicts of Interest disclosure
Dr. Cysique reports no disclosure/no conflict of interest
Dr. Łojek reports no disclosure/no conflict of interest
Mr. Theodore C.K. Cheung reports no disclosure/no conflict of interest
Dr. Cullen has no conflicts of interest to disclose
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Abstract

Objective: To propose a set of internationally harmonized procedures and methods for assessing neurocognitive functions, smell, taste, mental, and psychosocial health, and other factors in adults formally diagnosed with COVID-19 (confirmed SARS-CoV-2+ WHO definition).

Methods: We formed an international and cross-disciplinary NeuroCOVID Neuropsychology Taskforce in April 2020. Seven criteria were used to guide the selection of the recommendations' methods and procedures: (i) Relevance to all COVID-19 illness stages and longitudinal study design; (ii) Standard, cross-culturally valid or widely available instruments; (iii) Coverage of both direct and indirect causes of COVID-19-associated neurological and psychiatric symptoms, (iv) Control of factors specifically pertinent to COVID-19 that may affect neuropsychological performance; (v) Flexibility of administration (telehealth, computerized, remote/online, face to face); (vi) Harmonization for facilitating international research; (vii) Ease of translation to clinical practice.

Results: The three proposed levels of harmonization include a screening strategy with telehealth option, a medium size computerized assessment with online/remote option, and a comprehensive evaluation with flexible administration. The context in which each harmonization level might be used is described. Issues of assessment timelines, guidance for home/remote assessment to support data fidelity and telehealth considerations, cross-cultural adequacy, norms and impairment definitions are also described.

Conclusions: The proposed recommendations provide rationale and methodological guidance for neuropsychological research studies and clinical assessment in adults with COVID-19. We expect that the use of the recommendations will facilitate data harmonization and global research. Research implementing the recommendations will be crucial to determine their acceptability, usability and validity.

Keywords

COVID-19; neuropsychological functions; assessment; guidelines

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Since December 2019, the world has been grappling with escalating cases of *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2) infections leading to previously unknown *Coronavirus Disease* – COVID-19. By 15th of April 2021 – there were nearly 140 million confirmed cases of infection with the SARS-CoV-2 and almost 3 million deaths from COVID-19 (for up-to-date data see Word Health Organization, WHO 2021a).

Within a few months of the initial SARS-CoV-2 infections detected in Wuhan, physicians in charge of ill patients observed that the disease involved multiple organs besides the lungs, including the heart, liver, gut, peripheral nerves and the brain (Yang et al., 2020). A retrospective observational case series of 214 consecutive hospitalized patients with laboratory-confirmed diagnosis of SARS-CoV-2 (Mao et al., 2020), showed that neurological involvement was frequent (in 36% of 214 patients and in 45% of those with severe disease versus 30% in those with non-severe disease). Various cerebrovascular events (e.g., ischemic stroke, intracerebral hemorrhage, cerebral venous sinus thrombosis) are described as the most prominent COVID-19-associated neurological symptoms. This is followed by inflammatory CNS syndromes (e.g., encephalitis, encephalomyelitis). Peripheral neurological disorders (e.g., Guillain-Barré) and variants are less common (Frontera et al., 2020; Paterson et al., 2020; Varatharaj et al., 2020). SARS-Cov-2 may change the risk of stroke through an enhanced systemic inflammatory response, hypercoagulable state, and endothelial damage in the cerebrovascular system (Abootalebi et al., 2020). Frequent but typically less severe neurological symptoms include headache, dizziness, anosmia, and ageusia (Frontera et al., 2020; Helms et al., 2020). Anosmia and ageusia are reported even in patients whose presentation is not severe enough to warrant hospital admission or who are otherwise asymptomatic (Gane, Kelly, & Hopkins, 2020). In some cases, the involvement of the nasal epithelium may only reflect local inflammation. However, trafficking of viral particles and protein, in addition to SARS-CoV-2 RNA to the CNS cannot be excluded (Meinhardt et al., 2021).

Across the pool of retrospective studies on COVID-19, new-onset psychosis, affective disorders, altered mental status including agitation, and dysexecutive symptoms have also been reported (Helms et al., 2020). Some of these neuropsychiatric symptoms were linked to premorbid status (e.g., dementia), while others represented *de novo* symptoms (Varatharaj et al., 2020). Among the emerging prospective studies of COVID-19, one key finding is the relatively high prevalence of PTSD, depressive and anxiety symptoms (Bo et al., 2020; Xiang et al., 2020). While such high prevalence may be associated with pandemic stress and higher anxio-depressive symptoms across the community (Ettman et al., 2020), the possibility of immune-related or direct SARS-CoV-2 brain impact cannot be excluded at this stage (Troyer, Kohn, & Hong, 2020). PTSD is known to occur in patient groups who undergo severe and critical illness, especially ICU survivors, those who are intubated and mechanically ventilated, and ultimately those that experience delirium (Marra, Pandharipande, & Patel, 2017). An association between delirium and PTSD has been described recently in COVID-19 (Kaseda & Levine, 2020). Depression, anxiety, and PTSD can be associated with various neuropsychological deficits (Marcopulos, 2018) which will complicate the differential diagnosis of long-term neurocognitive effects of COVID-19 (Kaseda, & Levine, 2020). Finally, the rate and extent of recovery (chronic effects of COVID-19 on the CNS and the newly recognized "Long-COVID"), and potential increased risk for long-term neurodegenerative effects and neuropsychological sequelae are yet to be investigated (De Felice, Tovar-Moll, Moll, Munoz, & Ferreira, 2020; Wilson & Jack, 2020).

SARS-CoV-2 neuropathogenic mechanisms are thought to be multifactorial, including possible direct and indirect effects of the virus in the CNS (Frontera et al., 2020; Koralnik & Tyler, 2020). Evidence for the presence of SARS-CoV-2 RNA in the CNS and associated morphological changes (such as thromboembolic ischemic infarction of the CNS), specifically in the brain stem, have been shown (Meinhardt et al., 2021). Viral load of 5.0 to 59.4 copies per cubic millimeter was also reported in the brain sections from the medulla oblongata, the frontal lobes and olfactory nerves, obtained from 16 patients who died with COVID-19 (Solomon et al., 2020). Inconsistencies in the detection of SARS-CoV-2 in the CNS remain. This may be due to the dynamics of the infection in relation to when samples were obtained, and/or the fact that viral load and neural infectivity have a non-linear relationship (Yi et al., 2020).

In the acute phase, progressive respiratory involvement can lead to Acute Respiratory Distress Syndrome (ARDS), which is itself associated with a high risk of hypoxia and concomitant cognitive and psychiatric sequelae; this represents one of the main indirect pathways to brain damage in COVID-19 (Ellul et al., 2020; von Weyhern, Kaufmann, Neff, & Kremer, 2020; Wu et al., 2020). Acute hypoxic injuries were detected in the cerebrum and cerebellum in 18 patients who died with COVID-19, with loss of neurons in the cerebral cortex, hippocampus, and cerebellar Purkinje cell layer (Solomon et al., 2020).

Severe forms of COVID-19 illness requiring intensive care unit (ICU), intubation and ventilation may be associated with further immune, inflammatory and vascular brain damage. Secondary effects such as ICU delirium and possible long-term cognitive disorders are further observed and may be related to CNS invasion, inflammation, other organ failure and induction of sedatives (Kotfis et al., 2020).

The picture, course and long-term consequences of COVID-19 are modified by many factors. Serious health complications and the death toll from infection is greater among older individuals (>60 years), those with underlying medical conditions (including hypertension, obesity, chronic lung disease, diabetes, and cardiovascular disease). COVID-19 may also have a distinct course and impact in patients with pre-existing neurological, psychiatric, and immune conditions including schizophrenia (Fonseca et al., 2020; Kozloff, Mulsant, Stergiopoulos, & Voineskos, 2020), mild cognitive impairment, Alzheimer's disease, Parkinson's disease, multiple sclerosis (Matías-Guiu et al., 2020), and HIV-associated neurocognitive disorder (Levine, Sacktor, & Becker, 2020). Poverty, living in densely populated neighborhoods of lower socioeconomic status, a higher prevalence of comorbid diseases, and poor accessibility to health care facilities and services are further risk factors for contracting the virus, as well as negative health outcomes (Bialek et al., 2020; Laurencin & McClinton, 2020; Public Health England, 2020; Raifman & Raifman, 2020).

The above data indicate that as a result of many pathological factors and mechanisms associated with COVID-19 people recovering from that disease may experience cognitive, emotional and behavioral problems that require a referral to neuropsychology and/or neuropsychiatry services. It is not known how long these problems may persist, but for a certain number of COVID-19 survivors it may even be a life-long impairment, significantly influencing everyday life.

Neuropsychologists have already signaled urgent needs for developing research as well as clinical practice services for COVID-19 survivors (Postal et al., 2021; Sozzi et al., 2020; Wilson, Betteridge, & Fish, 2020). These studies, and mounting evidence from neurological studies (Taquet et al., 2021) support the hypothesis that COVID-19 may lead to neurocognitive disorders. One study included a sample of over 84,000 individuals who were coincidently participating in another study amid the COVID-19 pandemic (Hampshire et al., 2020). This UK study revealed that individuals who recovered from suspected or confirmed COVID-19 performed significantly worse on tests in multiple cognitive domains compared to people who did not suffer from COVID-19. This deficit was evident in hospitalized COVID-19 survivors, but also amongst individuals who did not receive hospital treatment. However, the study had significant methodological limitations in determining what may have been due to COVID-19 versus any other causes of impairment. Zhou et al. (2020) in China, Wuhan, examined cognitive functions (i.e., attention, memory, processing speed, executive functions and perceptual abilities) in 29 hospitalized patients who recovered from COVID-19 and 29 closely matched controls. They found impairment of sustained attention in the clinical group and a significant relationship between reaction time and inflammatory level as indicated by C-reactive protein.

Almeria, Cejudo, Sotoca, Deus, and Krupinski (2020) described cognitive disorders in 35 patients (aged 20 to 60) with confirmed COVID-19, without any previous neurological or psychiatric diseases. The patients were examined in-person, in 10 to 31 days after hospital discharge, using a set of standardized neuropsychological tests. Individuals presenting headache, anosmia, dysgeusia, diarrhea and those who required oxygen therapy had lower scores in memory, attention and executive function tests as compared to asymptomatic patients. Marked disorders (scores 2 SD below appropriate norms, controlling for age and education) were noted in the domains of memory, attention and semantic fluency (in 2 patients [5.7%]), in working memory and mental flexibility (3 [8.6%]), and phonetic fluency (4 [11.4%]). Anxiety and depression indicators were significantly related to subjective cognitive complaints.

Finally, an Australian study (Darley et al., 2020) conducted in a community sample (only 10% hospitalized) found low rate of neurocognitive impairment (9%) two months after recovering from COVID-19 illness on the Cogstate Test Battery measuring visual learning, speed of processing, attention/working memory and executive functions. However, 24% showed impairment on the NIH Toolbox Odor Identification test, and this was associated with neurocognitive impairment. Further, there was an association between moderate to severe initial neurological symptoms and continued subtle neurocognitive changes. More research is needed to confirm the observed cognitive impairment after COVID-19, relate it to neuroimaging data, and describe the persistence of deficits.

In response to the urgent needs associated with possible neuropsychological consequences of COVID-19, we formed the NeuroCOVID International Neuropsychology Taskforce in April 2020, with the goal of developing recommendations for harmonized standard neuropsychological methods and procedures/protocols to determine the prevalence, pattern and incidence of neurological and neuropsychological symptoms associated with COVID-19 in adults. The use of similar, harmonized assessment methods will help to combine data on COVID-19 from different sources. As of April 2021, the group has 107 members from 18 countries (see Figure 1).

Neuropsychological knowledge and methods can play a key role in understanding the prevalence, profile and nature of COVID-19 neurological and psychiatric symptoms. They may also contribute to the development of clinical management and facilitate development of rehabilitation guidelines for patients with COVID-19-related neurological disorders worldwide. There are currently no definitive standards for neuropsychological (i.e., cognition, motor functions, global-, mental- and psycho-social health, olfaction and taste) assessment of patients with COVID-19. A lack of standards will lead to disparate results which will be difficult to interpret as the methods and procedures will not be comparable and have unreliable associations with disease processes and biomarkers. This could result in inconsistent management guidelines, inadequate policies and poor outcomes for patients.

COVID-19 is a *new* disease. It is complex in that different (both direct infection and indirect) mechanisms may be responsible for neuropsychological dysfunctions. The range and severity of neurological symptoms are varied and potentially affect the entire neuraxis (Paterson et al., 2020). Developing research protocols that appreciate this complexity will have important clinical repercussions. The social lockdowns make standard in-person neuropsychological assessment practice difficult or impossible, even in countries with developed neuropsychological services. While awaiting a global vaccine and its roll-out, neuropsychologists adapted to the COVID 19 pandemic by modifying their services and adapting their assessments using telehealth – audio or video conferencing technologies (Bilder et al., 2020; Postal et al., 2021). This adaptation also necessitates a shift in standard methods of neuropsychological research of patients infected with COVID-19.

Since COVID-19 is a global pandemic, we must develop harmonized methods and procedures that are globally relevant and promote health equity just as we strived to do for HIV infection. Our recommendations must be applicable across various settings and work in low-middle and high-income countries. Building capacity to address such diverse objectives is fully embraced as one of the major goals of these recommendations.

To provide standard and harmonized neuropsychological methods and procedures for research in patients with COVID-19 infection and potential translation to clinical practice we apply the following selection criteria:

A. Methods appropriate for measuring the consequences of COVID-19, in order to:

- Measure the range and severity of COVID-19-associated neuropsychological dysfunctions (i.e., direct and indirect causes of COVID-19-associated neurological and psychiatric symptoms)
- Differentiate neuropsychological impairment from psychological distress
- Measure consequences at different phases of disease (acute/infectious, subacute, chronic) that fit requirements of longitudinal study design.
- Consider premorbid and comorbid effects, performance validity, and other factors that may affect neuropsychological performance in a manner specific to patients with COVID-19.

B. Methods and procedures adaptable to the pandemic social lockdown, and patients' quarantine status, or patient's hospitalization and alertness status (e.g., ICU versus ambulatory).

- Telehealth, computerized, remote/online, pen and pencils assessments options
- Screening strategies, medium size evaluation, comprehensive assessment options

C. Methods and procedures appropriate for international purposes:

- Selection of tests with evidence for cross-cultural validity or widely available instruments
- Guidelines or other considerations to promote valid cross-cultural test translation/adaption, as well as data fidelity.

To facilitate the implementation of the recommendations, the context in which each harmonization level could be used is described. Issues pertinent to required training level for administration and scoring, assessment timeline, guidance to support (remote) data fidelity, norms and impairment definitions are also described.

To address our aims, we propose three levels of harmonization of neuropsychological examination methods and procedures in COVID-19. Each level of harmonization covers a different level (from minimal, medium, to comprehensive) of neurocognitive, mental and psychosocial functions, and other important factors for describing medical and demographic characteristics. Harmonization level 3 was designed to represent a close equivalent to clinical practice.

Recommendations for Harmonization Level 1

General Assumptions

Harmonization Level 1 (HL1) is focused on research and clinical contexts requiring brief screening either remotely or in-person, adaptable to various health settings and the health/infectious status of the patient. It is also based on tools that have global applications and are inexpensive for cognition, sensation, and mental health; with administration requiring minimum training. HL1 is designed to fit a baseline assessment to a potential prospective longitudinal observational study; it can also serve as a stand-alone cross-sectional study design. The recommendations of an exact set of measures and variables will enable a single dataset and data merging for international comparisons and global epidemiological data - a minimum common dataset and associated code-book for the HL1.

Recommendations for Application

Patient's infectious status.—Eligible participants include SARS-CoV-2 seropositive patients (see WHO case definition at WHO 2021b) in the early phase of the disease, including asymptomatic individuals), as well as more advanced stages of the disease including patients presenting progressive respiratory involvement and focal/systemic inflammation. In these phases, it is very important to take into account the medical history to assess whether remote or bedside testing should be conducted at all. HL1 should only be conducted when a patient is fully able to participate in testing.

Intensive Care Unit (ICU) status.—Can be in ICU, any exams require personal protective equipment (PPE) in ICU settings and depends on local capacity to handle exams in ICU.

Time of testing for hospitalized patients.—Assessment of cognition should be completed around the time of discharge, ideally before.

Quarantine status.—Can be in quarantine or no quarantine.

Patient's alertness status.—Test should only be completed when the patient is fully able to do the testing via brief assessment of CNS symptoms.

Setting.—Telehealth, in-person with PPE. Considering pandemic-related limitations in research and clinical activities, the HL1 protocol can avoid in-person face-to-face contact through use of remote assessment methods. Thus, HL1 facilitates studying participants in the infectious phase who are (self-)quarantined, isolated or hospitalized.

Testing type.—Brief/screen.

Level of required training for administration and scoring.—Minimal.

Control group.—SARS-CoV-2-negative individuals can be recruited as the control group. Control group should be matched on demographics, health characteristics, quarantine, and hospitalization setting.

Table 1 summarizes the HL1 protocol.

Recommended Measurement Methods

Demographic inventory and medical history questionnaires.—Refer to the material provided in Supplemental Material 1 either via link access or copy of the material when authorised. We recommend the use of the Case Report Form (CRF) developed by the COVID Neuro-Network (access to the CRF requires a registration at Brain Infectious Global COVID-Neuro Network, 2021). We strongly recommend completing all the demographic and medical data sections of the CRF. The laboratory data sections are optional. This CRF includes CNS symptoms using the Glasgow Coma Scale (GCS) and the Modified Rankin Score, provided in Supplemental Material 1. We recommend documenting acute confusion states using the Confusion Assessment Method (CAM), also included in Supplemental Material 1.

Neurocognitive screens.—Montreal Cognitive Assessment 5-Minute Protocol (MoCA-5, Wong et al., 2015) is the short form of the Montreal Cognitive Assessment (MoCA), which was originally developed to screen for vascular cognitive impairment and dementia (Nasreddine et al., 2005; O'Driscoll & Shaikh, 2017; Wong et al., 2015), but later research covers various other neurological conditions (Hebert, Day, Steriade, Tang-Wai, & Wennberg, 2017; Phabphal & Kanjanasatien, 2011; Rodrigues, Gouveia, & Bentes, 2020). The four items of the shortened protocol cover attention, verbal learning and memory (with delayed recall), executive functions/language, and orientation. The advantage of the test is that it could be used in teleneuropsychology. A shortcoming is that visuo-spatial abilities would not be assessed. The full form has been translated and validated in 27 languages with most of them having norms provided (Mast & Gerstenecker, 2010). MoCA-5 is also available with alternative versions in English, French, Italian and Chinese. Its cultural sensitivity among racial and ethnic minorities has been researched (Milani, Marsiske, Cottler, Chen, & Striley, 2018; Milani, Marsiske, & Striley, 2019; O'Driscoll & Shaikh, 2017). The test is freely accessible, though test users are recommended to complete an official online training and certification in order to administer and interpret the MoCA and its various short forms.

While the MoCA-5 could be a preferred choice for quick screening in-person or in teleneuropsychology, domains such as attention and executive functions are abbreviated. A solution would be to consider the 22-point telephone Montreal Cognitive Assessment (T-MoCA, suggested cut-off = 18/19; Pendlebury et al., 2012), sometimes referred to as the "Blind MoCA" (Wittich et al., 2010). It essentially removes the visual related items from the full MoCA, and thus could cover the rest of the cognitive domains in all the languages in which MoCA has been validated. Its limitations, as pointed out by the test co-developers, are the lack of published validations with remote testing and norms for key groups of interest (Phillips et al., 2020).

Alternatively, we recommend the The Brief Test of Adult Cognition Telephone (BTACT; Tun & Lachman, 2006), though it is important to note that this tool has been recommended only for research. See legend of Table 1 for further details.

Cognitive symptoms.—The Patient's Assessment of Own Functioning (PAOFI) is a well-validated self-report questionnaire (Chelune, Heaton, & Lehman, 1986). The PAOFI covers cognitive domains such as memory function, language and communication, sensory and perceptual function, use of hands, and also provides a summary score. The PAOFI has been translated into multiple languages (HIV Neurobehavioral Research Program, 2020 see also Supplemental Material 1).

Smell/taste questionnaire.—This is a very brief set of questions adapted from The Smell and Taste component of the National Health and Nutrition Examination Survey (NHANES) 2013–2014, which can be easily adapted/translated. The questionnaire is provided in Supplemental Material 1.

Mental and psychological health questionnaires.—This step includes *Global health* assessment with the widely used – MOS 36-Item Short-Form Health Survey (SF-36) and the assessment of psychological health using the Depression, Anxiety and Stress (DASS-21) short form. Both instruments have been translated and adapted in many languages.

Recommendation for Harmonization Level 2

General Assumptions

Harmonization Level 2 (HL2) can be used as a first follow-up assessment post-acute infection. The set of measurement methods proposed at this level enables a more in-depth examination equivalent to a medium size research battery, which would also enable collaborative projects. Clinically, it could also serve as a more in-depth screen. This harmonization level also incorporates some flexibility for the tests' administration mode (telehealth and in-person) and attempts to minimize the testing duration. At this level, harmonization is achieved by recommending a set of selected tools, and recommending the coverage of specific cognitive, sensory, global and psycho-social domain areas. Additionally, availability of adaptations/translation and cross-cultural validity is documented. At this level, objective olfaction testing is also recommended.

Recommendations for Application

Patient's infectious status.—Negative (HL2 testing is deferred until the patient has recovered). Eligible participants are no longer infectious as proven with a SARS-CoV-2-negative result. HL2 should only be conducted when the patient is fully able to participate in testing.

Time of testing for hospitalized patients.—Assessment of cognition should be completed close to the time of discharge.

Quarantine status.—Quarantine or no quarantine

Patient's antibody status.—Documented if possible

Patient's alertness status.—As for a standard neuropsychological assessment

Setting.—Telehealth by video call, remote online testing, in-person/in-clinic (PPE), maximizing ventilation (e.g., open windows).

Testing type.—5–20 minutes screens; 3–10 minutes questionnaires

Level of required training for administration and scoring.—Closely follow the available manual guidelines and use supervised administration training when indicated

Control group.—SARS-CoV-2-negative individuals (no history of a positive test) can be recruited as the control group. Control group should be matched on demographics, health characteristics, quarantine, and hospitalization setting.

Table 2 summarizes the HL2 protocol.

Recommended Measurement Methods

The aim of HL2 is to examine the effects of COVID-19 on neurocognition, olfaction, taste and psychological well-being in greater detail. HL2 can assist in providing a more robust estimate of the potential disease-related neurocognitive impairment prevalence, but it cannot be considered a comprehensive assessment. HL2 is a medium size assessment, with remote options (although with some caveats for cognitive computerized testing). Where a longitudinal study has used HL1 as a study screen, HL2 outcome scores may be adjusted for performance on HL1. For participants who are unable to perform computerized neurocognitive testing (e.g., because of lack of appropriate hardware), HL1 assessment protocol is recommended. At HL2, options for remote completion of questionnaires are also proposed. We recommend clearly documenting the role of any informant in assisting questionnaire completion. We also recommend that the examiner dedicates some time with the participant/patient over the phone or face to face to clarify any responses on these questionnaires as appropriate. Finally, at this level we recommend the inclusion of performance validity tests (see supplemental file 5 for further guidance). COVID-19 is a widespread condition affecting a wide range of people. Ensuring that measurements of cognitive performance are valid is therefore essential.

Demographic inventory and medical history questionnaires.—We recommend using the same protocol as for HL1 and complementing the basic demographic data with more extensive testing of premorbid abilities. See also Supplemental Material 2.

Neurocognitive testing.—The cognitive domains of interest include those affected in a wide range of neurological and psychiatric conditions to capture potential direct COVID-19 effects on the brain as well as potential indirect effects: 1) Attention/working memory; 2) Executive function; 3) Motor function; 4) Processing speed; and 5) Learning and memory. HL2 remote testing is possible through online self-administration, but we recommend checking with the test providers whether this will fit your study population. In case of conflict with national health guidelines on telehealth, or wide variability of internet access and hardware suitability in your study population, we advise that you conduct the neurocognitive testing in-person. The other option is to repeat the HL1 protocol via telephone, and the rest of the HL2 protocol using telehealth or in-person assessment. Thus, using some flexibility in your protocol, you may be able to conduct a minority of tests/questionnaires in-person and use telehealth for the remainder. The rationale for the neurocognitive test selection includes, i). tools that are widely used with well-developed training manuals; ii). tools used internationally that have several language versions with evidence of cross-cultural validity and for some use in resource-limited settings; iii). and tools that have good criterion validity and test-retest reliability. Construct validity for standard neuropsychological tests was not retained as a selection criterion but is documented in supplemental material 2. The computerized format was primarily chosen to facilitate test administration (including by trained non-specialists), integrated data capture, and automatic scoring. The computerized format also facilitates multi-site studies. Lastly, we considered the availability of large normative datasets for optimal interpretation of performance. Supplemental material 2 includes detailed information about the four neurocognitive computerized tests, all available on tablets/iPad: Test My Brain (TMB); Cogstate Computerized Battery; NeuroScreen; and the NIH Toolbox Cognition and Motor Batteries.

Literacy, quality of education & premorbid ability and additional neuropsychological measures.—Literacy, quality of education and pre-morbid abilities can be documented via a demographic interview to which standard tests of reading or reasoning may be added. Careful consideration of the person's native language and level of education is needed to interpret test performance. The study scope might require additional neuropsychological tests, which we have also documented in supplemental material 2. The Grooved Pegboard Test could be used for motor functions or, alternatively, the 9-hole Pegboard Test is part of the recommended NIH Toolbox - Motor.

Cognitive symptoms.—Use HL1 protocol or consider other options provided in Supplemental Material 2. Specific consideration should be given to the timelines covered by these questionnaires, which may not fit the timeline of an acute infection with a range of recovery such as COVID-19.

Smell/taste questionnaire.—We recommend the longer version questionnaire adapted from the Taste and Smell component of the NHANES 2013–2014, which can be easily adapted/translated. This is provided in Supplemental Material 2.

Objective smell/taste testing.—Olfactory disturbances are commonly observed in COVID-19. Therefore, at HL2, we recommend the objective testing of olfaction because it is well established that self-report is not reliable, although this may not be the case for an acute infection such as COVID-19. We recommend the use of standard tests, selected based on their validity to determine anosmia and ageusia at various levels of granularity, the availability of good normative data, and some evidence of cross-cultural adaptation. Test details and access are described in Supplemental Material 2. The quickest olfaction tests may be adapted to remote online testing using a webcam, plus mailing of the scratch and sniff cards.

Mental and psychosocial health questionnaires.—We recommend using the HL1 protocol and, time permitting, adding a wider array of mental and psychosocial health questionnaires (see supplemental material 2 for details). Per current mental health literature in COVID-19, symptoms of PTSD, anxiety, depression, and fatigue may be the most important to screen. Careful consideration of mental health risk is needed if sending psychological questionnaires remotely; the scoring should be immediately interpreted using remote technologies to flag and follow-up with patients at high risk of distress.

Activities of Daily Living (functional) assessment (ADL).—It may be useful to assess Instrumental Activities of Daily Living (IADL), particularly for hospitalized cohorts, which typically have more severe COVID-associated neurological symptoms. Indeed, it is important to document the everyday functioning relevance of any acquired neurocognitive impairment. This also represents a first step towards rehabilitation strategies when needed. Traditional tools for IADL assessment are based on a set of pre-determined activities which may not be relevant to some individuals, depending on their gender, age, educational status and specific activity engagement (Sikkes, de Lange-de Klerk, Pijnenburg, Scheltens, & Uitdehaag, 2009). Traditional IADL measures also have low cross-cultural validity and poor psychometric properties for both criterion validity of IADL impairment and detection of decline upon repeated testing (Sikkes et al., 2009). We therefore recommend the use of recent instruments which have addressed some of these challenges (see Supplemental Material 2). These new instruments also have screening versions and several languages versions and offer methods for developing cross-culturally validated versions (Dubbelman et al., 2020; Jutten et al., 2018).

Recommendations for Harmonization Level 3

General Assumptions

Harmonization Level 3 (HL3) is akin to a standard, in-person comprehensive neuropsychological assessment for which we recommend a set of standard neuropsychological tests including performance validity tests. Objective olfaction and taste testing is also recommended.

Recommendations for Application

Patient's infectious status.—HL3 testing is deferred until the patient recovers. Eligible participants are no longer infectious as proven with a SARS-CoV-2-negative result.

Time of testing for hospitalized patients.—Assessment of cognition should be completed close to the time of discharge.

Quarantine status.—No quarantine.

Patient's antibody status.—Should be documented if possible.

Patient's alertness status.—As for a standard neuropsychological assessment.

Setting.—In-patient, in-clinic face-to-face (no/partial PPE), telehealth may be used for parts of the assessment.

Testing type.—Comprehensive, 2–4-hour sessions with breaks as appropriate.

Level of required training for administration and scoring.—Clinical Neuropsychology training, psychometricians.

Control group.—SARS-CoV-2-negative individuals (no history of a positive test) can be recruited as the control group. Control group should be matched on demographics, health characteristics, quarantine, and hospitalization setting.

Sanitary considerations for an in-person examination.—Mask and gloves should be used when appropriate in a dedicated room which would be disinfected after each patient. Test materials would also need to be disinfected (see Postal et al., 2021).

Table 3 summarizes the HL3 protocol.

Recommended Measurement Methods

The aim of HL3 is to examine in more detail the permanent, long-term and transient characteristics of COVID-19 effects on neurocognitive functions. Such a comprehensive assessment is critical to establish a solid rehabilitation strategy in patients with moderate to severe neurological/neuropsychological symptoms. HL3-in-person assessment comprises a selection of well-known standard neuropsychological tests, in addition to the olfactory and taste tests described in HL2. The primary cognitive domains of interest at HL3 are common to HL2, and so HL2 and HL3 may be combined when desirable. HL3-remote testing options represent a more robust estimate of the potential disease-related neurocognitive impairment prevalence at this stage of the disease than HL2 testing. If a study has used HL1 as a screen or even HL2, HL3 outcome scores can be adjusted for previous performance. For participants who are unable to undergo computerized neurocognitive testing, the HL1 over-the-phone assessment protocol can be repeated. At HL3, depending on the level of physical and possible cognitive difficulties a participant/patient may experience, some or all questionnaires may be done at home, but we recommend clearly documenting the role of any informant in assisting their completion. We also recommend that the examiner dedicates time with the participant/patient face-to-face to clarify any responses on these questionnaires as appropriate. For this more extensive assessment, we strongly recommend the inclusion of performance validity tests (see Supplemental files 5).

Demographic inventory and medical history questionnaires.—In line with the harmonization aim of our recommendations, we advise using HL1/2 protocols and supplementing as appropriate (e.g., depending on your study/patient population) with a more extensive assessment of demographics, socio-economic and cultural factors. Please consult Supplemental Material 2, where you will also find suggestions on assessment of premorbid abilities.

Neurocognitive testing.—Supplemental Material 3 presents a detailed description of a standard neuropsychological battery. This covers core domains for HL1 and HL2 and goes well beyond to cover the complex neurological syndromes that have been described whether directly due to COVID-19 or due to associated and underlying comorbidities. Addition of specific tests is warranted for other patient populations who have also been diagnosed with COVID-19 (e.g., Parkinson's disease).

Literacy, quality of education & premorbid ability.—Use HL2 protocol and see Supplemental Material 2.

Cognitive symptoms.—Use HL1 protocol and consider other options provided in Supplemental Material 2. The history taken prior to the comprehensive assessment is important to consider, to allow a nuanced interpretation of responses to the questionnaires (particularly with regard to symptom timelines).

Smell/taste questionnaire.—Use HL2 protocol.

Objective smell/taste testing.—Use HL2 protocol. The short or long version of the proposed assessments could be used, depending on your study questions (e.g., focusing on perception rather than cognition), time constraints, and participant/patient engagement and fatigue.

Mental and psychosocial health questionnaires.—We recommend including HL1 and HL2 protocols (see Supplemental Material 2). Depending on study-related factors (e.g., focusing on mental health more than cognition; different study populations) or patient-related factors (e.g., time constraints, engagement and fatigue), you may select more targeted mental and psychosocial health questionnaires.

IADL.—For HL3, ADL assessment is strongly recommended. Consult HL2 information above and Supplemental Material 2.

Harmonization Levels: Cross-Cultural and Disparities Issues

The recommendations attempt to deal a priori with the international aspect of the epidemic. In this section, we therefore provide guidance on how best to use the recommended tests across diverse populations. Although our recommended tests are used internationally, cross-cultural appropriateness and availability of tests are crucial. Within local contexts, tests should be selected and administered considering the background characteristics of the target population to avoid violating fairness in testing (Aghvinian et al., 2020; International Test Commission, 2019). Cultural and sociodemographic factors (sex, age, education, ethnicity, socio-economic status) impact neuropsychological test performance (Brickman, Cabo, & Manly, 2006). Neuropsychological tests must therefore be culturally appropriate with regard to language use and test stimulus items. Age- and education-appropriate norms are necessary to determine whether a person's performance falls outside the normal range (Fernandez, 2019; Mitrushina, Boone, Razani, & D'Elia, 2005). Where such normative data are not available, a well-matched control sample is required (Casaletto & Heaton, 2017). These issues are particularly pertinent in low- and middle-income countries (LMIC) where few neuropsychological measures have been adapted and validated, and normative data are scarce.

Key issues for the implementation of the current recommendations across settings include access to human resources and expertise, technological and socioeconomic considerations, and availability and adaptation of study measures. Access to human resources and expertise varies between and within countries. Where there is a lack of expert- and human-resources (e.g., trained neuropsychologists) in LMIC, clinical or general psychologists may be involved. Lay people can also be trained to do assessments under supervision by a psychologist, allowing delegation to less specialized health care- or lay-workers, particularly when combined with automated, easy-to-use tests that can be performed on a phone or a tablet (e.g., NeuroScreen; Magidson et al., 2017; Robbins et al., 2018). Mental health screening must similarly be supervised by a clinical/neuropsychologist or psychiatrist familiar with the local setting. Distance supervision applies in locations without direct access to specialists, in line with the current Taskforce guidelines.

Access to technology and connectivity also varies across settings and use of mobile health applications must be viewed in light of available resources. In LMIC access to computers or tablets may be limited, for example, but access to smartphones is ubiquitous. The high cost of mobile data in some settings may limit ability to complete online assessments. These issues must be carefully considered during study design. Availability and affordability of study measures vary across countries and so, if possible, tests that are in the public domain should be used. With regard to test use and adaptation, if the recommended tools have not been adapted, existing original or adapted tests that measure the same construct should be used. If no adapted/validated measure is available, best practice guidelines for test adaptation and translation should be followed (e.g., a committee/team translation or forward- and back-translation (Harkness & Schoua-Glusberg, 1998; Vallejo-Medina et al., 2017). Test publishers must be contacted timeously for permission to translate tests. All measures (e.g., mental health, medical history, etc.) must be translated and adapted to reflect regional language and cultural practices.

The recommended neuropsychological measures included in HL1–2-3 to a large degree reflect the neuropsychological test battery widely used in HIV studies, both in high income countries (HIC) and LMIC (Kabuba, Anitha Menon, Franklin, Heaton, & Hestad, 2017; Nyamayaro, Chibanda, Robbins, Hakim, & Gouse, 2019), suggesting applicability of tests across diverse settings. There are, however, some considerations to keep in mind when selecting tests for the purpose of describing the neurocognitive presentation associated with COVID-19. In particular, tests that measure cognitive constructs and global levels of functional capacity must be culturally valid. Below we provide further comments on particular measures from HL1–2-3 that may require cross-cultural adaptation in some settings (Table 4); for computerized tests, see also Supplemental Material 2.

Harmonization Levels: Norms, Impairments Ratings, and repeated neuropsychological testing

Practitioners should carefully follow the standard scoring instructions and guidance for interpretation of all the tests, using standard materials obtained from accredited test providers. Practitioners are responsible for determining whether the tools we have recommended are either in the public domain and thus free to use and reproduce, or whether the tools need to be purchased from accredited providers, some of which require specific qualifications to access.

Norms.

We recommend the use of published nationally representative normative data appropriate to your study sample age, education/SES and sex, in addition to race/ethnicity and rural/urban living when possible. When nationally representative normative data are not available, we recommend using a demographically and geographically comparable control sample and, if capacity and expertise permits, developing norms.

Controls.

Data collection in a local, demographically representative and healthy control group is recommended. The published norms should be checked in your local sample to assess if they "work", that is, whether they correct for demographic effects. Depending on the study question, controls may also be from a clinical comparison group, for example patients who have been through ICU.

Neurocognitive impairment levels.

In research studies, methods to determine levels of cognitive impairment (e.g., as cut-off scores on screens, or normative standard scores on one or more neuropsychological tests) should be clearly described and linked to a well-established nomenclature of performance levels. Extra attention should be given to computerized cognitive tests, and associated literature using those tests, to determine standard levels of deficits. Reporting level of "neurocognitive impairment" in controls is advised for transparency and better interpretation of the burden of the disease in COVID-19 samples.

Smell/taste impairment levels.

The current recommendations include both questionnaires and smell/taste tests. The suggested measures are commonly used in general as well as clinical populations. They can be used to quantify smell loss or describe the severity of alteration caused by COVID-19. While we selected tests with available norms in several countries, it is still possible that these norms may not be appropriate for your population. In this case we recommend that you compare results from your SARS-CoV-2-positive sample to a demographically comparable SARS-CoV-2-negative or asymptomatic control group, and/or longitudinally in order to track within-patient changes across the stages of the disease. Diagnosing impairment should be done with caution and follow the standard impairment grading of the original norms.

Repeated Neuropsychological testing.

COVID is an evolving condition which starts with an acute infection phase, whether symptomatic or not. It is likely that a large part of the forthcoming research will be longitudinal to assess disease recovery on several occasions. Because of this, longitudinal data analysis and considerations of issues associated with neuropsychological repeated testing will be critical to characterise the neurocognitive complications of COVID-19. Please consult supplemental file 6 for further guidance.

Consideration of contributing, confounding and incidental medical, psychological, lifestyle and demographic factors (beyond the norms corrections).

We advise carefully documenting any pre-existing (e.g., systemic, immune, neurological or psychiatric) or comorbid (e.g., stroke, hypoxia, lung disease) conditions to determine to what extent they may impact on neurocognitive, sensorimotor, and psycho-social health. Besides traditional demographics, it is important to note whether the participant is literate or may have been diagnosed with a learning disability. These various factors should be carefully documented, and their effects tested as appropriate.

Feedback reports for research.

It is advised to produce individual feedback reports when conducting a research study. Such reports should ideally be sent to the participant's doctor of choice so that the information is interpreted in the relevant clinical context. Reports should provide a detailed description of tests/questionnaires administered, modality of testing (in-person; remote: over-the-phone / computer-based) and involvement of the research/clinical personnel (personnel present in-person / remotely; or self-administered by the participant / informant). For remote assessment, reports should additionally provide information on the testing platform, describe non-standard administration procedures and related limitations (e.g., limited understanding of participant's vision, hearing or level of familiarization with testing devices). Research reports employing (at least a part of) the currently recommended neuropsychological protocols are welcome to include a citation of this paper. However, the description of the testing protocol should still be provided in order to enable comparisons with other sites. Additionally, references can be made directly to the Harmonization level 1–3 (basic/full; in-person/remote) and selected measures. Citation will further enhance visibility of the original research papers and support building comparable databases for future meta-analysis and between-site data sharing. Clinical reports should further describe the potential impact of the administration procedure, and its alterations, on the proposed diagnosis and (if applicable) recommended treatment.

Guidelines for Home/Remote Assessment to Support Data Fidelity and Telehealth Considerations

Although there are no formal published standards for remote assessment and telehealth in neuropsychology, several national organizations have issued professional practice guidelines in recent months (American Psychological Association, 2020a; Interorganizational Practice Committee, 2020; The British Psychological Society, 2020). Key points from these guidelines are summarized in Supplemental Material 4. The APA has published a useful (though US-focused) checklist to help practitioners prepare for clinical sessions with these considerations in mind (American Psychological Association, 2020b). Practitioners must adhere to test publisher rules regarding copyright and sharing of materials (e.g., Pearson Assessment, 2020).

A meta-analysis of teleneuropsychology administration compared with in-person (Brearly et al., 2017) found that the difference between videoconference and in-person performance was very small (Hedges $g = -0.03$), and not statistically or clinically significant. Results were less consistent in patients aged over 75 and in situations with slower internet connection speed. The authors concluded that videoconference administration of verbally mediated tasks by qualified professionals using existing norms was supported, and the use of visually-dependent tasks may also be considered, but motor-based tasks require further investigation.

Concluding Remarks and Future Directions

The long-term impact for COVID-19 survivors in the months and years post-recovery is, as yet, unknown; however, there are suggestions that based on the prevalence of critical illness alone, post-COVID-19 long-term cognitive impairment will be significant in some patients (Needham, Chou, Coles, & Menon, 2020). Neuropsychologists will benefit from approaching assessment and rehabilitation of individuals after COVID-19 from a holistic point of view, considering cognition, emotional functioning, behavior, and potential socioeconomic pandemic impact as interacting variables that impact on functional independence, quality of life, and emotional well-being. It is with this framework in mind that the current recommendations have been prepared.

The NeuroCOVID Neuropsychology International Taskforce will promote these recommendations through our research and collaborations. The group anticipates that the recommendations will facilitate multi-site and international collaborations and we encourage colleagues from HIC to develop studies that assist research in LMIC when appropriate. Implementation research regarding the acceptability, usability and validity of the recommendations will be critical to their uptake and the Taskforce welcomes feedback on potential improvements and adjustments to inform refinement of the recommendations. It is important to note that these recommendations apply only to adult research and practice; analogous recommendations for neuropsychological research with children infected with SARS-CoV-2 are urgently needed.

The Taskforce will start the development of a minimum dataset and associated code-book protocol, including a proposal for protocol registration. This minimum dataset will first be based on the lowest common denominator as developed in the recommendations (i.e., Harmonization level 1) and we hope to then include other harmonization levels. This effort will include secure online data storage and good practice guidelines for the participating sites. It is planned that individual researchers will access the database after contacting the coordinators and proposing the analysis to be conducted. Funding will be sought for the development and maintenance of the database.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank all members of the NeuroCOVID International Taskforce. New members are welcome, and membership enquiry can be sent to Dr. Cysique (lcysique@unsw.edu.au) and Dr Łojek (emilia@psych.uw.edu.pl) by email. The group works from the Slack platform at: https://neurocovidinssig.slack.com/?redir=%2Fgantry%2Fclient#/. The taskforce is also represented at the International Neuropsychological Society (INS) as a Special Interest Group (https://www.theins.org/sigs/). The statement that the opinions/data/perspectives belong solely to the authors and the NeuroCOVID International Taskforce and may not necessarily represent the viewpoint of INS. We thank Dr. Susan McPherson for bringing to our attention the question of performance validity tests.

Funding sources

- Dr. Cysique is supported for her NeuroCOVID research by the Peter Duncan Neuroscience Unit, St. Vincent's Applied Medical Research Centre, Sydney, Australia, and the Alfred Hospital in Melbourne, Australia.
- Drs. Łojek, Hansen, Holas, and Malinowska are supported by the Faculty of Psychology, Warsaw University, Poland
- Dr. Muñoz-Moreno is supported by the Fundació Lluita contra la SIDA, Germans Trias i Pujol University Hospital, Barcelona, Catalonia, Spain
- Mr. Theodore C.K. Cheung is supported by the Ontario Graduate Scholarship, Canada.
- Dr Gouse is supported by the Fogarty International Center 1K43TW010361-01
- Dr. Silva (A.R.) is supported by the Portuguese Agency of Science and Technology.

Appendix 1.: Authors' contributions

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Dr Jonathan Evans	Institute of Health and Wellbeing, University of Glasgow	Contributed to manuscript writing and editing/ proof-reading and provided input on revisions and responses to reviewers.
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Notes. The taskforce is coordinated from a dedicated Slack platform. All members have access to all Slack channels, and all are able to share, propose and access the material, including the manuscript as it evolved via a Slack-Google Drive link. The SIG co-chairs have administrative access to Slack. SIG members are required to become INS members to join, per INS policies. For the current recommendations, members were asked to self-nominate for leading manuscript sections using the Team channel. More than one member could be a section author. The co-chairs led the synthesis from all the co-authors and all co-authors have reviewed the paper, including two senior researchers who are native English speakers.

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Figure 1.
The Taskforce international representation
Notes. taskforce includes 107 Members from the following countries: USA (52 Members), Australia (15), Poland (7), Canada (5), Netherlands (5), South Africa (4), UK (4), Spain (3), Belgium (2), Norway (2), Chile (1), Finland (1), Germany (1), Greece (1), Israel (1), Malaysia (1), Mexico (1), Zambia (1), Portugal (1) [numbers correct as of February April 27th, 2021].

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Table 1.

Harmonization Level 1 Protocol

#	Domain	Format	Completion time (min.)	Mode of administration
1	Demographic inventory Use COVID-19 Neuro Network CRF	CRF Questionnaire	5–10	Self Can be aided by informant In-person or telehealth* Email or secure mailing of questionnaires may be used* Use medical records Use information from treating doctors
2	Medical history questionnaires includes CNS symptoms Use COVID-19 Neuro Network CRF and added scales	CRF Questionnaire	10–20	
3	Neurocognitive screens	Standard screening test**	10–20	In-person or telehealth
4	6-items- Smell and taste questionnaire	Questionnaire	1–2	In-person or telehealth* Email or secure mailing of questionnaires may be used* Self Can be aided by informant
5	Cognitive symptoms questionnaire	Questionnaire	4–5	
6	Mental and Psychosocial health	Questionnaire	5–8	

NB: the protocol material is available in Supplementary Material 1

*Some information may be filled out by participants/patients and their informants at their convenience within 3 days of the screen exam.

**We also recommend the Brief Test of Adult Cognition Telephone (BTACT; Tun & Lachman, 2006) as a potential alternative to the MOCA-5/T-MoCA as the standard screening test. The BTACT is composed of the Rey Auditory Verbal Learning Test (RAVLT), Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) Digit Span Backwards, Category Fluency test, Red/Green test, Number series and Backward counting. The BTACT was originally developed to monitor the effects of aging on cognition; thus, it assesses wider neurocognitive function than dementia screening tools (Bodien et al., 2018; Dams-O’Connor, Landau, Hoffman, & St De Lore, 2018). The administration time is 15–20 minutes. The BTACT has high validity with other pen & paper tests and has good reliability, hence the in-person test version can be alternatively used when possible. The testing procedure includes accuracy checks and time of completion. There are four alternate versions (1 original + 3 alternatives) to minimize practice effects on repeated assessments. The subtests examine episodic memory, working memory, reasoning, verbal fluency, and executive function and there is an option to calculate a composite score. The English, Spanish and French versions of the BTACT have been normed (Lachman, Agrigoroaei, Tun, & Weaver, 2013). Importantly, the BTACT can be accessed and used for free with permission by the developer (version A-B contact Dr. Lachman; versions C-D contact Dr. Silverberg).

Table 2.

Harmonization Level 2 Protocol

#	Domain	Format	Completion time (min.)	Mode of administration
1	Demographic inventory Use COVID-19 Neuro Network CRF	CRF Questionnaire	5–10	Self Can be aided by informant In-person or telehealth * Use medical records Use information from treating doctors
2	Medical history questionnaire includes CNS symptoms Use COVID-19 Neuro Network CRF and added scale	CRF Questionnaire	10–20	
3	Neurocognitive testing	Computerized Standard Test: 4 options	10–15	In-person Telehealth is possible if carefully adapted, but guidance from test developers is strongly recommended See also dedicated sections below
4	Smell and taste questionnaire	Questionnaire	5–10	In-person or telehealth * Email or secure mailing of questionnaires may be used * Self Can be aided by informant
5	Cognitive symptoms questionnaire	Questionnaire	4–15	
6	Mental and Psychosocial health	Questionnaire	5–20	
7	Objective olfaction/taste testing	Standard Test: 4 options	3–5	In-person Can be adapted for telehealth
8	Literacy, quality of education & premorbid ability and additional neuropsychological measures	Standard Test		In-person Can be adapted for telehealth
9	Everyday activities	Questionnaire	5	In-person or telehealth * Email or secure mailing of questionnaires may be used * Self Can be aided by informant
10	Performance Validity	Standard Test	3–10	In-person or telehealth *

NB: the protocol material is available in Supplementary Material 2

*Some information may be filled out by participants/patients and their informants at their convenience within 3 days of neuropsychological exam.

Table 3.

Harmonization Level 3 Protocol

#	Domain	Format	Completion time (min.)	Mode of administration
1	Demographic inventory Use COVID-19 Neuro Network CRF Adapt/include socio-economic and cultural factors	CRF Questionnaire	10–30	Self Always consider informant In-person Telehealth may be used * Use medical records Use information from treating doctors
2	Medical history questionnaire includes CNS symptoms Use COVID-19 Neuro Network CRF and added scales Supplement with history taking	CRF Questionnaire	10–60	
3	Neurocognitive testing	Standard neuropsychological test battery Combine with HL1 & HL2 as appropriate	60–90	In-person Part of the assessment may be adapted for telehealth but guidance from test developers is strongly recommended (see also dedicated section on telehealth)
4	Smell and taste questionnaire	Questionnaire	5–10	In-person Telehealth may be used * Self Can be aided by informant Email or secure mailing of questionnaires may be used *
5	Cognitive symptoms questionnaire Supplement with history taking	Questionnaire	5–20	
6	Mental and Psychosocial health Supplement with history taking to target key information and select more questionnaires.	Questionnaire	5–30	
7	Objective olfaction/taste testing	Standard Test: 4 options	5–20	In-person Can be adapted for telehealth for some tests
8	Literacy, quality of education & premorbid ability	Standard Test	5–10	In-person Can be adapted for telehealth for some tests
9	ADL Supplement with history taking to target key information and select more questionnaires.	Questionnaire +Informant	5–30	In-person Telehealth may be used * Email or secure mailing of questionnaires may be used * Self + Should be aided by informant
10	Performance Validity	Standard Test	3–10	In-person or telehealth *

NB: the protocol material is available in Supplementary Material 2 and 3

*Some information may be filled out by participants/patients and their informants at their convenience within 3 days of neuropsychological exam.

Table 4.

Cross-cultural considerations and recommendations for instruments proposed in HL 1–2-3

Domains	Tools	Considerations and recommendations
Cognitive screeners (HL 1–2)	MOCA-5/T-MoCA	+ More culturally appropriate telephonic cognitive screening measure. − Recommended over BTACT.
	BTACT	+ Relies partially on instruments with cross-cultural validity testing (e.g., RAVLT; Digit backwards). − Number-Series task compromised validity for some LMIC populations (social and formal educational differences). − Must adjust the BTACT cut-off score when some tasks are not suitable for inclusion (e.g., Number-Series task).
Functional Screeners (HL 1–2)	Activities of Daily Living (ADL) Scales	+ ADLs are culturally bound and vary significantly between and within settings. + Local/national tools are more suitable than global measures, if available (Pashmdarfard & Azad, 2020). + Lawton Instrumental Activities of Daily Living Scale (IADL) has several cultural adaptations (Dubbelman et al., 2020; Ng, Niti, Chiam, & Kua, 2006; Siriwardhana, Walters, Rait, BazoAlvarez, & Weerasinghe, 2018; Stone et al., 2018). − If not available, develop and validate tools using Siestke et al. methods.
Standard neuropsychological tests (HL 2–3)	*BVMT-R (visuospatial learning and memory)*	− Some subjectivity associated with scoring with an inter-rater agreement of ~60% (Caneda, Cuervo, Marinho, & Vecino, 2018). − Must adhere strictly to standard scoring guidelines to reduce bias.
	HVLT-R (verbal learning and memory)	− A culturally and linguistically appropriate version of the HVLT-R must be used − In the absence of an appropriate version of the HVLT-R, a culturally suitable substitute e.g., Rey Auditory Verbal Learning Test (RAVLT), California Verbal Learning Test (CVLT) or Free and Cued Selective Reminding Test (FCSRT) (Lim et al., 2009) can be used.
	Category fluency	+ More normative data exist for the Animal category than the Fruits and Vegetables category. The former is therefore recommended.
	Premorbid ability	− LMIC lack normative data to reliably estimate premorbid intelligence. − Within countries, disparities in terms of socio-economic status must be taken in account (Shuttleworth-Edwards, 2016) in the validation processes of these measures. − Premorbid IQ should only be assessed if appropriate normative data are available accounting for age, education and SES status.
	Performance Validity	− See Supplemental file 5. − Collection of data in appropriate control group will be needed in many locations as cross-cultural versions of such tests are lacking