

Evaluation of upper limb perception after stroke: a prevalence and longitudinal study with the new Affected Limb Perception Questionnaire (ALPQ)

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Abstract

Background

Following a stroke, patients may suffer from alterations in the perception of their own body due to an acquired deficit in body representations. While such changes may impact their quality of life as well as recovery, they are not systematically assessed in clinical practice. This study aims at providing a better understanding of the prevalence, evolution and impact on recovery of upper-limb body perceptions (BPs) alterations following stroke. In addition, we will investigate associations among BPs alterations items, their associations with the sensorimotor functions, upper-limb usage, damages in brain structure and connectivity.

Methods

We developed a new tool named ALPQ (for Affected Limb Perception Questionnaire) to address the present study objectives. It assesses subjective disturbances in the perception of the affected upper limb (UL) following stroke, by measuring several dimensions, namely: anosognosia for hemiplegia, anosodiaphoria for hemiplegia, hemiasomatognosia, somatoparaphrenia, personification of the affected limb, illusion of modification of physical characteristics (temperature, weight, length), illusory movements, super- or undernumerary limb, upper-limb disconnection, misoplegia, and involuntary movement. This study combines a cross-sectional and longitudinal design. The ALPQ will be administered to minimum 60 acute and 100 sub-acute stroke patients. When possible, patients will be followed up to the chronic stage. Complementary evaluations will be administered to assess patients' sensorimotor and cognitive functions as well as upper-limb activity, and brain lesions will be analysed.

Discussion

The ALPQ is a new tool to evaluate patient's body perceptions which has the advantages to cover a broad range of BPs distortions, to be compatible with the clinical context, and to have a quantitative approach. This study will provide a better understanding of BPs alterations following stroke: their prevalence and evolution, as well as their associations with sensorimotor deficit, cognitive profile and spontaneous arm activity, brain lesions and recovery. Ultimately, the results could support the personalization of rehabilitation strategy accordingly to patients' UL perception to maximize their recovery.

Trial registration

<https://osf.io/p6v7f>.

Background

Information concerning our own body, coming from different afferent signals (e.g., touch, proprioception, visual signals), are processed and integrated by the central nervous system (e.g.[1]) into neural body representations. These representations encode how the body is sensed (e.g. in terms of the shape, size, weight) and experienced (i.e. sense of ownership, agency, emotional feeling towards the body parts) (e.g. [2–4]). These aspects are regrouped under the term “body perceptions” (BPs) in this paper.

Body representations are not fixed, but constantly updated as a function of the bidirectional sensorimotor flow of information between the body and the brain [5]. Following a cerebrovascular accident, sensorimotor deficits may alter this flow, leading to distortions in body representations that result in a change in the way patients perceive their body, i.e. BPs’ distortions (e.g. [1, 6–8]). For example, stroke patients suffering from somatoparaphrenia spontaneously deny that their contralesional limb belongs to themselves, even pretending it is someone else [9]. Less severe cases report altered feeling towards the contralesional limb when explicitly asked [10, 11]. In addition, alterations in the perceived dimension of the contralateral limb were revealed by different tasks [12, 13].

BPs’ distortions may impact patients’ recovery [10] and quality of life [8, 14]. However, contrary to sensorimotor functions, BPs are not systematically assessed in clinical routine practice, so that a deficit may be unnoticed unless the patients spontaneously report it.

This has led to a currently limited understanding of BPs alterations in terms of prevalence, patients’ profile (i.e., associated deficits and lesions), evolution and impact on the recovery of other functions. We believe that this shortcoming may be explained by a lack of tools sensitive enough to assess BPs, but also simple and easy to use to be compatible with clinical environment and routines. In the next paragraphs, we outline these current open issues and present the approach proposed in this study to address such limitations.

Prevalence of alterations in BPs after stroke

To investigate the prevalence of BPs alterations following stroke, previous studies focused on one specific deficit at a time, such as anosognosia for hemiplegia [15] or somatoparaphrenia [16]. However, this does not provide a broad view of the extent and diversity of BPs alterations. The overall prevalence of BPs deficits after stroke has only been seldom investigated. Schwoebel and Coslett [6], Raimo and co-authors [17], Razmus [18] as well as Bassolino and co-authors [13] estimated altogether from 39.5–81% of stroke patients with a deficit in at least one component of BPs. This wide range is explained by the different experimental tasks used in each study, targeting different BPs, as well as by the different profiles of the patients included, varying by the phase of the disease (acute, sub-acute and/or chronic), the inclusion [18] or exclusion [6, 17] of bilateral lesions, the selection of specific lesion lateralisation (e.g. only right brain damage patients [11, 16]) or specific deficits that are considered to be associated to particular BPs distortions (e.g. only patients with motor deficits [13]). This emphasizes that the choice of restrictive inclusion criteria, necessary to reach certain objectives of previous studies, limits our understanding of the prevalence of BPs alterations in the stroke population.

Moreover, it must be noted that the above reported prevalence mainly estimated through task-based assessment may not reflect the subjective, explicit experience of the body of the patients. Using a questionnaire to assess the subjective experience of patients on multiple items targeting explicit feelings towards the affected limb (e.g. I feel my arm as “foreign”, or “dead”), Bassolino et al. found that 100% of 60 chronic stroke patients with unilateral motor deficit reported at least two negative feelings towards their affected upper-limb [13].

Evolution of BPs alterations

Although BPs distortions can be long lasting (e.g. [10, 13, 19]), they are more frequently observed in the acute phase after stroke (e.g. see [20] for anosognosia for hemiplegia). One of the reason is that some disorders, like anosognosia for hemiplegia or somatoparaphrenia, can resolve a few days (but also later) after stroke (e.g. [20]). Moreover, we suspect that after the first confrontations with therapists in earlier stages, patients may consider unnecessary or embarrassing to mention them spontaneously or to complain about them afterwards. Therefore, to get a comprehensive view of BPs alterations after stroke, it is crucial to study their evolution through the different stages of the disease (acute, sub-acute, and chronic).

Serrada et al. [14] investigated the evolution of some components of BPs in stroke patients from the acute to the chronic phase, using the Bath CRPS Body Perception Disturbance Scale (BPD) [21], initially developed for Complex Regional Pain Syndrome (CRPS) patients. They report that some BPs disturbances captured through the BPD scale in the acute phase improved one month after stroke, with no further improvement up to six months after stroke. While this result offers a first insight on a possible favourable evolution of some BPs alterations after stroke, the authors did not detail the results for each sub-component of the BPD scale, thus leaving interpretations related to specific BPs alterations impossible. On the other hand, using different assessment tasks, Crema et al. [10] showed that alterations in upper-limb BPs can still be present at the chronic stage and can be ameliorated following specific interventions. However, the study included patients at the chronic stage with no information on the earlier status, preventing conclusions about the evolution of BPs alterations through the different stages of the disease. The lack of other available studies highlights the need to further investigate the evolution of BPs alterations assessed with stroke-specific tools along the different phases of the disease and in relation with the recovery of other functions.

Relationship with sensorimotor deficits

Since the construction and update of BPs resides in the bidirectional flow of sensorimotor signals, it is critical to quantify the presence of sensory and motor deficits and to study their relationship with BPs alterations in order to better understanding their underlying mechanisms and their impact in patients' recovery. Serrada et al. [14] reported that distortions in upper limb perception strongly correlated with motor function impairment, but weakly correlated with superficial somatosensory and proprioceptive deficits. On the other hand, Crema et al. [10] reported that, in the chronic phase, distortions in body perception were associated with proprioceptive deficits. Although these studies provide some seminal

notions on this topic, the relationship between BPs and sensorimotor deficits remains to be better explored by assessing them along the different phases of the disease and with respect to recovery, in patients with a broad range of sensorimotor abilities.

Lesion correlates of body perception deficits

Finally, alterations in body perception after stroke may depend either “indirectly” on brain lesions causing sensorimotor deficits, or on lesions affecting brain areas or networks processing and integrating body signals to build or update body representations. The study of associations between BPs distortions and brain lesions has been frequently addressed by focusing on hemispheric lateralization (e.g. Raimo et al. 2021 [17]) or on structural lesions (of grey or white matter via voxel lesion symptom mapping, VLSM), thus identifying brain regions associated with a specific BPs alteration (e.g. [19, 22, 23]). More recently, new approaches studying the networks or their disconnections have been used (e.g.[24–26]), suggesting that network’s disconnection may better explain alterations in BPs than damage of discrete cerebral areas [1]. However, each of these studies focused only on a specific neuropsychological alteration (e.g. personal neglect, body ownership or anosognosia) without allowing comparison or combination of different BPs alterations.

Aim of the study

This project aims at better characterizing and assessing disturbances in the perception of the affected upper-limb following stroke by:

- i. estimating the prevalence and the severity of each potential distortions of BPs;
- ii. exploring the relationship of the observed BPs alterations between each other as well as with sensorimotor deficits and upper-limb activity;
- iii. assessing the evolution of BPs alterations and their impact on sensorimotor recovery and upper-limb activity;
- iv. characterizing structural lesions to specific brain areas or networks disconnections associated to deficits in BPs.

In the literature, the available tools to assess body perceptions are not suited to address the present aims. Indeed, previous studies propose tasks or questionnaires which focus mainly on specific BPs alterations (e.g. [16, 27]), include items not specific to alterations typically described in stroke populations [10, 14], have a qualitative approach (e.g. [8]), or limited sensitivity using limited scoring system such as binary answers (e.g. [10]) or Likert scale (e.g. [11]). For these reasons, we developed a new questionnaire to capture patients' explicit feelings towards their affected limb, the Affected Limb Perception Questionnaire (ALPQ).

Methods/design

Study design

This study combines a cross-sectional and a longitudinal design, summarized in Fig. 1.

Participants are recruited at different stages of the disease:

[T0] in the acute phase of stroke (up to 14 days after stroke event) in one stroke unit (University Hospital Lausanne (CHUV), Lausanne, Switzerland)

[T1] in the sub-acute phase of (> 14 days to 3 months after stroke) in 3 rehabilitation centers (University Hospital Lausanne (CHUV), Lausanne, Switzerland; Institution de Lavigny, Lavigny, Switzerland; Villa Beretta Rehabilitation Center, Valduce Hospital Como, Costa Masnaga, Italy).

In addition, sub-acute stroke patients seen at timepoint 'T1' will be invited for a follow-up visit:

[T2] before their hospital discharge (only if $T2 \geq T1 + 3$ weeks)

[T3] at the chronic phase (at 1 year \pm 180 days following stroke event, only if T2 evaluation has been completed)

Due to clinical organisation, this follow-up will be conducted systematically at one study site (Villa Beretta Rehabilitation Center), and with a limited number of patients at a second study site (the Institution de Lavigny).

Patients seen at the acute phase (timepoint T0) will not be followed-up at the sub-acute phase, unless they are hospitalized in one of the study rehabilitation hospitals where they will also be invited to participate in the sub-acute phase of the study.

A short version of the ALPQ (see b-ALPQ described hereafter) will be administered at T0 to study the prevalence of BPs alterations in the acute phase. A complete version of the ALPQ (see VAS-ALPQ described hereafter) will be administered at T1, T2 and T3 to evaluate the evolution of BPs deficits and their recovery.

Complementary evaluations to assess upper-limb activity as well as sensorimotor and cognitive functions are performed at \pm 7 days from the administration of the ALPQ in all phases (see Table 2 for the list of these tests).

In addition, brain lesion analyses will be conducted on available neuroradiological images at the acute stage (and/or early sub-acute stage) acquired for clinical purposes, whether MRI or Angio-CT scan.

INSERT FIGURE 1 around here

Study population / Participants

Patients fulfilling the following criteria are invited to participate in the study. Note that inclusion and exclusion criteria have been defined with the aim of being representative of the general stroke population

(i.e., including unilateral and bilateral lesions, with and without sensorimotor deficits) to better measure prevalence, while ensuring a correct administration of the ALPQ.

Inclusion criteria:

- Age \geq 18 years old.
- Diagnosis of stroke (\leq 14 days for the acute phase, 15 days to 3 months for the sub-acute phase).
- Ability to understand and respond to instructions (as determined by the clinician). Importantly, this includes the ability of the patient to be able to look at the contralesional limb OR to verbally indicate that he/she has understood that the question is not about the ipsilesional limb but the other limb.
- Sufficient understanding of verbal requests of French/Italian (all neuropsychological tests can be administered in French/Italian).
- Ability to understand the patient information sheet, and to sign the consent.
- In addition, for the VAS-ALPQ, the ability to indicate response on a vertical visual analogue scale is assessed prior administration of the ALPQ.

Exclusion criteria:

- Major neurological diseases other than stroke: neurodegenerative diseases (e.g. Parkinson's disease, dementia) or auto-immune diseases (e.g. multiple sclerosis) or meningoencephalitis or leukopathia.
- Patients with a diagnosed epilepsy before stroke that required surgery or medications.

Importantly, stroke-related epilepsy episodes are NOT an exclusion criteria (even if they are under medications).

- History of brain tumor.
- History of moderate or severe brain trauma (defined as Glasgow score $<$ 13 or post-traumatic amnesia $>$ 24h).
- Recurrence of stroke, if the last stroke event occurred within 6 months from the previous one. It is accepted only IF previous lesions occurred more than 6 months ago, wherever the lesions side(s).
- History or current psychosis (e.g. Schizophrenia) or eating disorders (in agreement with DSM 5 definitions).
- Unresolved somatosensory and/or motor deficit, unrelated to stroke, of any upper-limb (contralesional or ipsilesional). Importantly, sensorimotor deficit related to a past stroke event are NOT an exclusion criteria.

We aim at enrolling at least 60 eligible acute patients (at T0) and 100 eligible sub-acute patients (at T1). In order to estimate the prevalence of BPs distortions after stroke, the screening and enrolment is done consecutively. At the acute stage, all stroke patients seen by the neuropsychological service in a stroke acute unit will be screened. At the sub-acute stage, all stroke patients admitted to a hospital's rehabilitation units will be screened. The duration of enrolment is estimated to last between 18 to 36

months. A group of at least 30 age-matched healthy controls will also be evaluated to assess possible variability in the responses given on the VAS scale [16].

Measurements

The Affected Limb Perception questionnaire (ALPQ)

We developed a structured questionnaire to assess subjective disturbance in the perception of the affected upper limb (UL) following stroke.

We developed two versions of the questionnaire: (i) a short version (the b-ALPQ, b- for 'binary'), based on binary yes/no answers, compatible with acute patients' vigilance, fatigability and availability in an acute stroke unit and (ii) a standard version (VAS-ALPQ), for patients seen at later stages of the disease, which aims at providing a more sensitive and quantitative assessment of the deficits by using a continuous visual analogue scales (VAS). Other authors already shown the efficacy of VAS scales to detect and investigate body disownership after a brain lesion (Ronchi et al., 2020).

The questionnaire assesses a wide spectrum of BPs related alterations, listed in Table 1: it includes frequently documented alterations (e.g. anosognosia for hemiplegia, somatoparaphrenia) as well as additional less documented ones identified from our experience with stroke patients (namely upper limb disconnection, change in physical characteristics, illusory movements). The evaluation of additional BPs deficits (anosognosia for hemiasomatognosia, over-care for the upper-limb, etc.) were initially included in the questionnaire, but removed in order to keep the time of administration of the questionnaire compatible with clinical practice. Since some studies suggest that pain could alter body perception [28], and that it is a common symptom after stroke [29, 30], the ALPQ also assesses pain as control item.

INSERT Table 1 around here

Table 1
Items included in the b-ALPQ and the VAS-ALPQ

	b-ALPQ	VAS-ALPQ
	<i>yes/no</i>	<i>VAS</i>
Fatigue		X
Sadness		X
Anxiety		X
Most-affected limb		
1. Pain	X	X
2. Anosognosia for hemiplegia	X	X
3. Anosodiaphoria for hemiplegia	X	X
4. Hemiasomatognosia	X	X
5. Somatoparaphrenia	X	X
a) UL belonging to someone else		
b) UL not being human		
6. Personification of the affected limb	X	X
7. Illusion of modification of physical characteristics	X	X
a) Temperature		
b) Weight		
c) Length		
8. Illusory movements	X	X
9. Supernumerary /Undernumerary limb	X	X
10. Upper-limb disconnection	X	X
11. Misoplegia	X	X
12. Involuntary movements (lack of agency)	X	X
Less-affected limb		
1. Anosognosia for hemiplegia		X
2. Hemiasomatognosia		X
3. Somatoparaphrenia (UL belonging to someone else)		X

	b-ALPQ	VAS-ALPQ
Evaluation of altitudinal neglect		
Altitudinal neglect		X

The items are always presented in the same order, as listed in Table 1. In addition to the BPs alterations related items that are included in the b-ALPQ, the VAS-ALPQ includes three initial items to assess the general status of the patient at the moment of the administration: fatigue, sadness, and anxiety. Moreover, three BPs alterations related items regarding the less-affected upper-limb are administered as control items, after the evaluation of the most-affected upper-limb, as described in Table 1. Finally, altitudinal neglect (also called vertical neglect) [31–35] is evaluated at the end of the questionnaire. It is not assessed at the beginning in order to limit the risk of inducing a persistent response to the middle of the scales. A description of the altitudinal neglect assessment is available in Additional file 1.

In case of unilateral cortical lesion, the most affected upper limb is the one contralateral to the lesion, while in case of cerebellar lesion, the most affected upper limb is the ipsilesional one. In case of bilateral lesions, the limb with the highest sensorimotor deficits at T0 or T1 (or contralateral to the most affected hemisphere in the unlikely case of no sensorimotor deficit) is considered as the most affected one.

In the acute phase, patients are asked to report their feelings in the present and past 24 hours. In the sub-acute and chronic phase, the questions refer to the past 7 days.

In this study, the b-ALPQ is in French language, and the VAS-ALPQ in French and in Italian. Depending on the patient's condition and answers to the questionnaire, the b-ALPQ is administered in 5 to 10 minutes and the VAS-ALPQ in 20 to 50 minutes.

The b-ALPQ

The b-ALPQ is administered verbally to the patient i.e., the questions are read by the practitioner and the patient answers verbally with “yes” or “no” answers.

If the patient reports an altered BR sensation (i.e. “yes” answer), he/she is invited to further describe the characteristics of her/his altered sensation (if any), through structured questions, for the following items: somatoparaphrenia, personification of the affected limb, illusion of modification of physical characteristics, illusory movements, supernumerary/undernumerary limb, upper-limb disconnection and involuntary movements.

The VAS-ALPQ

In order to allow the questionnaire to be administered to patients suffering from visual hemineglect, the VAS are presented vertically and centred on the patient's midline, as previously described by other authors

[16]. A sentence is presented at the top and at the bottom of the scale, and the patient is asked to indicate her/his response in relation to the two statements (see Fig. 2.A.). The sentence describing a BR alteration is always positioned at the top of the scale, while the opposite one (i.e. describing no BR alteration) is positioned at the bottom. The top of the scale corresponds to a score of 14, while the bottom corresponds to zero (i.e. no alteration).

We developed an ad-hoc application in order to administer the VAS-ALPQ using a tablet. To run the app, we chose a Samsung Galaxy Tab A7, which has a symmetrical frontal layout and does not contain any element that could bias the attention of the patient towards the top or bottom of the screen.

For each item of the VAS-ALPQ, the examiner reads the top and bottom sentences of the VAS, pointing at them with the stylet. Then the patient answers the VAS directly on the tablet, using the same stylet (see Fig. 2.A.). If the patient's answer on the VAS is spatially close to the bottom (i.e. zero), the examiner asks the patient to verbalise her/his answer in order to understand whether s/he was aiming to report no alterations or a mild alteration (VAS > 0 but close to zero).

For each item of the VAS-ALPQ, in case of an answer indicating a BR alteration (any time the value of the corresponding VAS is > 0), the practitioner asks verbally the patient to rate on a 3-point scale the intensity and frequency of the reported sensation. In addition, similarly to the b-ALPQ, additional structured questions are asked verbally by the practitioner to guide the patient to further describe the characteristics of the reported sensation for the following items: somatoparaphrenia, personification of the affected limb, illusion of modification of physical characteristics, illusory movements, supernumerary/undernumerary limb, upper-limb disconnection and involuntary movements. The answers to these additional questions are collected directly on the application (see Fig. 2.B) and may also allow to detect a misunderstanding of an ALPQ item (e.g. if a very high frequency and intensity is reported in complementary questions, while a very low score on the VAS scale is indicated).

Before the administration of the VAS-ALPQ, two preliminary evaluations are performed to ensure that the patient will be able to answer the VAS-ALPQ and allow her/him to familiarize with the procedure: (1) the patient's ability to perceive the vertical line and discriminate its two extremities is evaluated by asking her/him to indicate the upper and lower extremities of a vertical line and to follow the line with the stylet; (2) the patient's understanding of the use of a VAS is verified with two examples. These examples do not concern the body and suppose that the patient answer at the upper extremity of the scale for the first example, and between the two extremities for the second example.

Instructions

Several key rules are followed when administering the questionnaire. For example, when asking the questions related to the upper-limb, the examiner points at the arm/hand saying "this arm/this hand" but never touches it, nor uses the pronoun "your" ("your arm/your hand"). This prevents to give tactile stimulation on the affected side or to perform a confrontation with a potential feeling of disownership. In order to administer the VAS-ALPQ to all patients in the same way, an instruction booklet was created

(indicating, for instance, when to accept a request from the patient to change her/his answer and how to record it).

INSERT FIGURE 2 around here

Complementary evaluations

Complementary evaluations are collected within ± 2 days to the administration of the b-ALPQ at T0, and within ± 7 days to the administration of the VAS-ALPQ at T1, T2 and T3. The following functions are assessed: a) *Somatosensation*, including superficial sensation, as well as static and dynamic proprioception; b) *Upper limb motor function*, including force, strength, spasticity; c) *Upper-limb activity* is assessed by patient's therapist in a 4-point Likert scale for all patients at T0, T1 and T2, as well as, at one study site (Villa Beretta Rehabilitation Center), with accelerometer bracelets on both wrists at T1 and T2; d) *Cognitive functions*, including memory, personal neglect, language, executive functions and upper-limb apraxia; e) *Anxiety and depression*. The full set of tests are listed in Table 2.

When applicable, the less-affected limb is always assessed before the most-affected limb.

The procedure for the administration of each complementary evaluations as well as the outcome measures are further described in Additional file 1.

INSERT Table 2 around here

Table 2
List of complementary evaluations collected at each timepoint

	STROKE PATIENTS				CONTROL SUBJECTS
	Acute	Sub-Acute		Chronic	
	<i>T0</i>	<i>T1</i>	<i>T2</i>	<i>T3</i>	
Affected Limb Perception Questionnaire					
b-ALPQ	X				
VAS-ALPQ		X	(X)	(X)	X
Somatosensory functions of the UL					
<i>Superficial</i>					
Tactile Detection (Em-NSA) [36]		X	(X)	(X)	
Sharp/Blunt discrimination (Em-NSA) [36]		X	(X)	(X)	
2-point discrimination test		Subgroup	Subgroup	Subgroup	X
<i>Proprioception</i>					
Dynamic (RASP) [37, 38]	X (finger only)	X	(X)	(X)	
Static (Thumb Localizing Test) [39]		X	(X)	(X)	
Motor function of the UL					
Grip strength* [40]		X	X	X	X
Fugl-Meyer UL [41]		VB	VB	VB	
Short Fugl-Meyer UL [42]	X	X	X	X	
Ataxia (item from the Fugl-Meyer UL)* [41]	X	X	X	X	
Modified Ashworth Scale [43]		X	X	X	
Motricity Index [44, 45]		VB	VB	VB	
ARAT [46]		VB	VB	VB	
Box and blocks [47]		VB	VB	VB	
9-hole peg test [48]		VB	VB	VB	

	STROKE PATIENTS				CONTROL SUBJECTS
	Acute	Sub-Acute		Chronic	
	<i>T0</i>	<i>T1</i>	<i>T2</i>	<i>T3</i>	
Physiotherapist's feedback	X	X	X	Subgroup	
Upper-limb activity					
Physio/Occupational therapist's feedback	X	X	X	Subgroup	
Spontaneous arm use (ARYS™ pro accelerometer bracelets)		VB	VB		
Body Representations					
FLUFF [49]		X	(X)	(X)	
Personal Neglect (BEN) [50]	X	X	(X)	(X)	
Bilateral Extinctions (BEN) [50]	X	X	(X)	(X)	
Neuropsychological evaluations					
MoCA [51]		X	Subgroup	Subgroup	X
Apples [52, 53]		X	(X)	(X)	
HADS [54]		X	X	X	
TICSf-12 (for French speaking sites) [55]		X	Subgroup	Subgroup	
AAT (for Italian speaking site) [56]		X	Subgroup	Subgroup	
Trail Making Test [57] /Color Trail Test [58]		X	X	Subgroup	X
RBMT faces or objects [59]		X	(X)	(X)	
Digit Span Forward and Backward [60–63]		X	Subgroup	Subgroup	X
Mahieux-Laurent's test for apraxia [64]		X	(X)	(X)	
Neuropsychologist/Speech therapist's feedback		X	X	Subgroup	
<i>T0, T1, T2, T3 = timepoint of evaluation of stroke patients</i>					
<i>* when feasible by the patient</i>					
<i>X = for all patients/subjects</i>					

	STROKE PATIENTS				CONTROL SUBJECTS
	Acute	Sub-Acute		Chronic	
	<i>T0</i>	<i>T1</i>	<i>T2</i>	<i>T3</i>	
<i>(X) = only for patients who did not have the maximum score at the previous timepoint</i>					
<i>VB = Performed only at one rehabilitation site (Villa Beretta Rehabilitation Center)</i>					
<i>Subgroup = Data collected only if evaluation is performed in routine practice or if time allows</i>					

Statistical Analysis

ALPQ items for which the patients showed to have not understand the question or contradicted him/herself when verbally formulating her/his answer will be excluded from the analysis.

Main statistical analyses

We aim at performing the main following analyses:

- i. The *prevalence* of each BPs alteration as assessed by the ALPQ will be determined at the acute (T0) and at the early sub-acute (T1) stages as the percentage of patient presenting the deficit on the total number of patients who answered the question. Such analysis will be run also in subgroup of patients of interests, such as with right / left brain lesion or with / without sensorimotor deficits. Comparisons in the prevalence at T0 and T1 and in the different subgroups will be run (e.g., via chi-squared or equivalent tests).
- ii. The *evolution* of BPs alterations across the various stages of the disease (acute, sub-acute, chronic) will be (a) studied by comparing the symptom presentation between T0 (with the b-ALPQ) and T1 (with the VAS-ALPQ) for each item of the questionnaire, and (b) quantified between T1, T2 and T3, by considering for each VAS-ALPQ item the reported value on the VAS (e.g. analysed through linear mixed models or ANOVA or equivalent non-parametric analyses, in case of non-normal data distribution).
- iii. *Associations* among BPs alterations items will be assessed (e.g. through multiple correlations, cluster analyses, or principal components analyses).
- iv. *The relation* between ALPQ scores and the results from complementary measures will be explored (e.g. through multiple regression models or linear mixed models)

Analyses will be performed on continuous VAS scores (or binary score for the b-ALPQ) of specific items or cluster of similar items (see above point iii), on cumulative score of all BPs alterations reported by the patient or on the most relevant and frequent BPs alterations.

Lesion analyses

After defining the scores of interests to quantify BPs deficits as a function of the analyses explained in the previous paragraph, a series of lesion analyses will be conducted.

To identify focal lesions significantly associated with BPs alterations, we will run voxel-based Lesion-Symptom Mapping analyses [65] on the level of BPs disturbances, after having regressed out lesion volume.

To reveal the correlates of BPs disturbance at the network level, further analyses based on structural or functional connections/disconnections using voxel lesion network mapping (e.g.[66]) and disconnection analysis (e.g.[26, 67, 68]) will be performed on the same behavioural index.

Discussion

To date, it is well accepted that stroke patients may suffer from a distorted perception of their body (e.g. [6, 18]). However, these deficits are not assessed systematically. This may be explained by a lack of tools to assess BPs alterations adapted to the clinical practice, as well as by a still limited understanding of the prevalence, evolution and impact of BPs alterations on the recovery of other functions.

A new tool to assess BPs alterations

To address these issues, we developed a new questionnaire, the ALPQ (Affected Limb Perception Questionnaire). With respect to previous studies using questionnaire to assess BPs (e.g. structured interview to assess asomatognosia [27]; the MUNA [11]; the ALEFq [10]; the BPD scale [14]), the ALPQ has been designed to have at least three distinctive features.

First, it covers a broad range of BPs distortions, by including items referring to the main alterations in BPs after stroke reported in literature, as well as additional less investigated items that we consider relevant on the basis of unstructured interviewed that we performed with stroke patients in preparation to this study and feedback from several clinicians consulted. This will allow us to assess the prevalence at the acute and sub-acute stages of a broad spectrum of BPs alterations after stroke and to track their evolution.

Second, the ALPQ is adapted to the clinical context. Both versions of the ALPQ can be used with a wide range of patients, even those suffering from aphasia who have preserved understanding, since the use of verbal answers (beyond “yes/no” for b-ALPQ and for the complementary questions of both ALPQ versions) are not mandatory (for the VAS-ALPQ a booklet to point at the corresponding answer of complementary questions was also created). The use of the tablet allows an efficient way to administer the questionnaire and collect the data. The ALPQ administration manual ensures reproducibility in the procedure. In addition, to allow assessing BPs in the acute phase and in stroke units, where time for evaluation and patients’ attentional resources are limited, we developed a short, binary version of the ALPQ (b-ALPQ). Although the b-ALPQ would be likely less sensitive than the VAS-ALPQ based on continuous scale (see next point), this is compatible with the clinical needs. On the other hand, the b-

ALPQ (which is aimed to be administered verbally) can also be used with patients suffering from major visual deficits and who may therefore not be able to answer the VAS-ALPQ.

Finally, the VAS-ALPQ exploits a quantitative approach based on visual analogue scales, recently proposed to be more sensitive to capture BPs alterations [16]. In addition, the items have been defined to balance negative with positive wording, to avoid biasing patients' responses [10]. This will allow the VAS-ALPQ to be robust in assessing the severity of distortions and monitoring their potential evolution, as well as to conduct powerful statistical analyses on the underlying associations with sensorimotor deficits and brain lesions.

While this study focuses on the stroke patients, the ALPQ can be adapted and used to assess BPs in other populations with sensorimotor disorders or diseases that can lead to alterations in BPs. Adapted versions of the questionnaire to other populations, i.e. patients with CRPS and multiple sclerosis, are in preparation.

Characterisation of BPs alterations following stroke

The adoption of the ALPQ and the design of the current study will allow us to investigate four important points to better understand BPs alterations following stroke.

First, this study will provide an estimation of the prevalence at the acute and sub-acute stage of the disease for the general stroke population. Traditionally, due to putative hemispheric specialization, BPs deficits are studied in right brain damaged patients (e.g.[11]), whereas other studies selected patients for the presence of sensorimotor impairments (e.g.[13]). Although, these subpopulations of stroke patients may indeed more likely suffer from BPs alterations, some studies show that BPs alterations are not limited to these cases (e.g. [17]). The eligibility criteria of the present study have been determined to enhance our understanding of BPs alterations in the general stroke population, without a priori selection in terms of patients' lesion localisation or sensorimotor deficit, while guaranteeing feasibility of patients' participation. Despite these broad eligibility criteria, we can still expect unbalanced groups between right and left brain injuries, as patients in the latter group are more likely to suffer from aphasia. If aphasia limits their understanding, they will not be able to participate in the study. Although some left-brain damage patients will be excluded for this reason, not limiting our observations to specific lesion laterality, nor sensorimotor impairment, represents an important opportunity to assess possible associations between different prevalence or severity in BPs alterations, hemispheric lateralization and sensorimotor deficits (see next point). This will also allow us to describe the complete clinical profile of patients showing BPs distortions.

Second, the administration of a battery of complementary evaluations assessing sensorimotor and cognitive functions as well as upper-limb activity will allow us to further characterize associations of BPs alterations with sensorimotor deficit, cognitive profile and spontaneous arm activity.

Third, with the longitudinal design of this study, we will provide insights into the evolution of BPs alterations up to the chronic phase of the disease, also in relation with spontaneous arm activity and

recovery of sensorimotor functions. While we expect to have a higher prevalence at the early stages, studies have shown that some alterations may be persistent (e.g. [10, 16]). It is worth noticing that because of the patients clinical flow, only a subset of patients seen at the acute stage (T0) will be transferred in one of the sub-acute study site. This implies that that most of the data obtained at the follow up in the chronic stage (T3) will have a correspondence in the sub-acute stage (T1), but not necessarily in the acute phase. Therefore, the evolution of BPs alterations will mainly be monitored between the early sub-acute (T1), late sub-acute (T2) and chronic (T3) stages.

Finally, the lesion analysis will provide insight into the anatomical basis of BPs alterations, but also their underlying network.

In conclusion, the present study aims at describing a broad picture of BPs alterations after stroke in the different phases of the disease and in relations with sensorimotor deficits, upper-limb spontaneous activity, brain lesions as well as recovery. This knowledge would potentially drive the development of new rehabilitative targeted and personalized interventions taking into account BPs disturbances to improve patients' functional outcome [8, 69].

List Of Abbreviations

ALPQ
Affected Limb Perception Questionnaire
b-ALPQ
binary ALPQ
VAS-ALPQ
Visual Analog Scale ALPQ
ALEFq
Affected Limb Explicit Feeling questionnaire
BPD scale
Body Perception Disturbance scale
BPs
Body Perceptions
MUNA
Motor UNawareness Assessment
VAS
Visual Analog Scale

Declarations

Ethics approval and consent to participate

This study is conducted in accordance with the Declaration of Helsinki and following ethics committee approval (Switzerland: CER-VD, project #2017-01588 ; Italy: Comitato Etico dell'Insubria, protocol number:

208 /2020). Informed consent is requested to all participants prior participation.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

There are no conflicts of interest associated with this study.

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Authors' contributions

SK and VB developed the ALPQ, with inputs from JF and MB. SK under the supervision of MB and AS and with the contribution of IM and JF, designed and set-up the study, and wrote the ALPQ manual and protocol. FM and EG provided guidance on the study design. All authors have read and approved the final manuscript.

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Figures

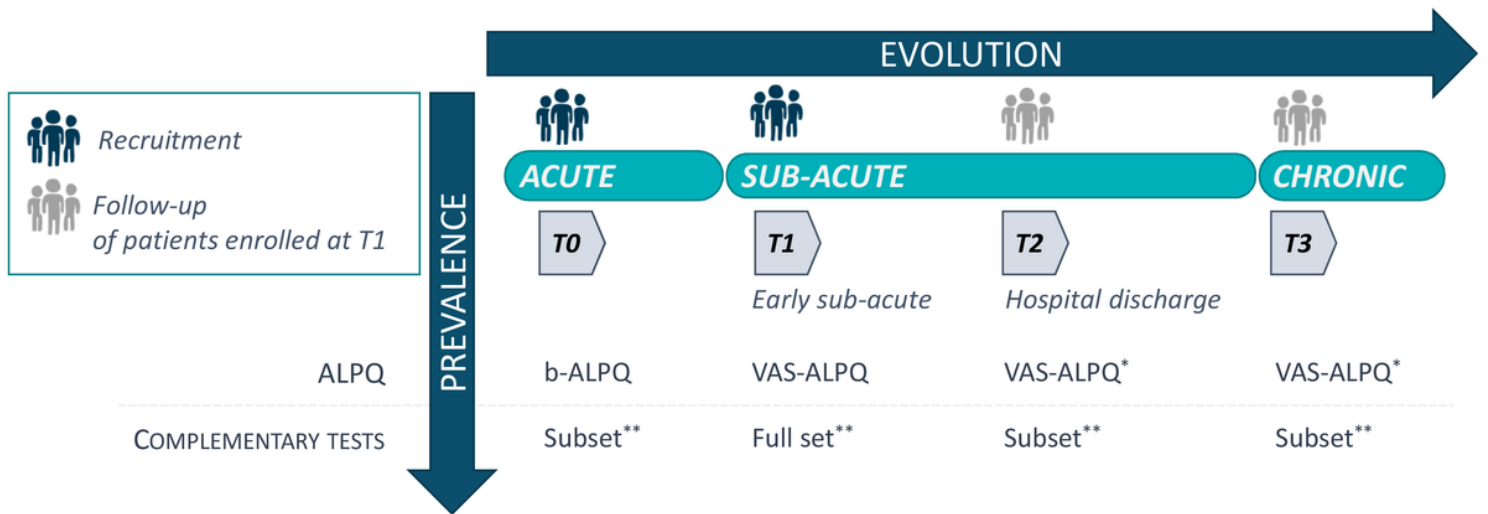


Figure 1

Illustration of the ALPQ study design. Patients are recruited at two timepoints: T0 (acute) and T1 (early sub-acute) ; Patients enrolled at T1 are invited for a follow-up visit at T2 (at their hospital discharge) and T3 (chronic phase) timepoints ; (*) The VAS-ALPQ is only performed if patient reported one positive symptoms to at least one item of the ALPQ administered at the previous timepoint ; (**) See Table 2 for the list of tests performed at each timepoint.

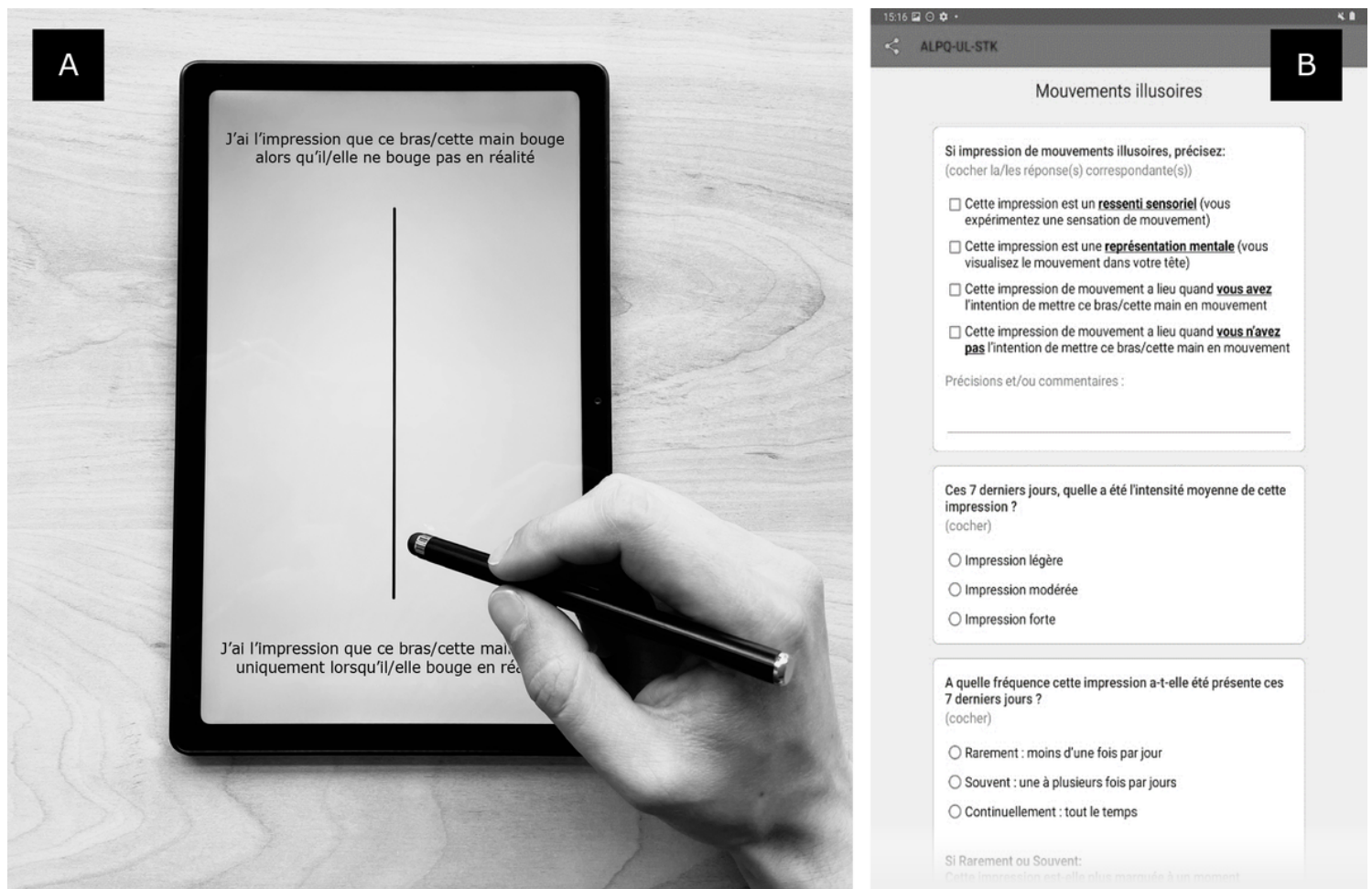


Figure 2

Example of administration of the VAS-ALPQ. (A) Patient answering with a styllet the VAS to evaluate *Illusory movements* in the French version of the questionnaire. At the top of the VAS: “*I feel that this arm/this hand is moving when in fact it is not*”. At the bottom: “*I feel like this arm/this hand only moves when it actually moves*”. (B) Example of complementary questions asked to patient in case s/he reports *Illusory movements*: further characteristics of patient’s impression (upper box), intensity (central box) and frequency (lower box).

Supplementary Files

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