New insights into the diagnosis, rehabilitation and understanding of hemineglect using new technologies

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Abstract

Hemineglect is one of the most frequent cognitive impairments after stroke, causing a major limitation for functional remission, with symptoms persisting years post-onset. Despite the extent of the impairment, a large part of the fundamental research and applied clinical practice has focused on the perceptive aspects of hemineglect, and overlooked links with action and action abilities. The aim of the present thesis was to bring new insights in the assessment, rehabilitation and understanding of the condition, combining perception and action measures. Throughout the thesis, an innovative sensitive and reliable robot test measuring visuo-spatial hemineglect and associated action kinematics was validated on stroke patients. Additionally, the thesis provided a novel hemineglect robot rehabilitation using a serious game, where game difficulty was auto-adapted in accordance to the patient's impairment severity. Finally, by using these technological tools, factors moderating the link between perception and action in hemineglect were identified.

Résumé

L'héminégligence est un des troubles cognitifs les plus fréquents à la suite d'un accident vasculaire cérébral et constitue un obstacle majeur à la rémission fonctionnelle des patients, qui présentent encore des symptômes plusieurs années après l'accident. Malgré l'ampleur du trouble, la majorité de la recherche fondamentale et de la pratique clinique est orientée vers les aspects perceptifs de l'héminégligence sans considérer ses liens avec l'action et les capacités motrices. L'objectif de cette thèse est d'approfondir l'évaluation, la rééducation et la compréhension de ce trouble en combinant des mesures de perception et d'action. A travers cet ouvrage, un test robotisé, innovant et sensible évaluant l'héminégligence visuo-spatiale et les propriétés cinématiques de l'action qui y sont associées a été validé sur des patients cérébrolésés. De plus, cette thèse apporte une rééducation robotisée novatrice utilisant un jeu sérieux, dont la difficulté est auto-adaptée en fonction de la sévérité du trouble du patient. Finalement, en utilisant ces outils technologiques, certains facteurs modérant le lien entre la perception et l'action dans l'héminégligence ont été identifiés.

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General introduction

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General introduction

Imagine waking up in the morning and getting yourself ready to go to work. It resembles any other morning, but something just seems off. Not just something, but almost everything you do seems slightly off. You get dressed without putting your left arm in the left sleeve of your shirt. You shave or apply make-up only on the right side of your face. You have your usual breakfast, but you cannot open the jam jar and you only eat the toast on the right side of your plate. As you leave the house, you only put your right shoe on, and it curiously takes forever to tie your shoelaces. You are late to work because you struggled to read the time on a clock, and somehow you seemed to drive around in circles, instead of driving straight to work. As you walk in the corridor of your office, you bump into several walls. You finally sit at your desk, but you cannot find the cup of coffee that someone just prepared for you! This imaginary morning provides a glimpse of the struggles faced by hemineglect patients.

In most cases, hemineglect, also called unilateral spatial neglect, is a condition that results from a stroke, either ischemic (i.e., blockage of a blood vessel) or haemorrhagic (i.e., rupture of a blood vessel) (Kamtchum Tatuene et al., 2016; Mackay, Mensah, Mendis, & Kurt, 2004). In Europe, stroke affects approximatively 1.1 million people a year, with a large majority of ischemic strokes. The prevalence rate is 5% in people younger than 75 years, and over 10% in people older than 80 years (Béjot, Bailly, Durier, & Giroud, 2016). Stroke survivors often suffer from significant consecutive morbidity leading to 33% of hospital re-admission within the first year of stroke (Lainay et al., 2015). Sensory, motor and cognitive deficits following stroke lead to a massive detrimental impact on individual functioning (Mercier, Audet, Hébert, Rochette, & Dubois, 2001), with the presence of hemineglect demonstrated as a predictor of poor functional outcome (Jehkonen et al., 2000).

There have been a large amount of diagnosis tests and treatment techniques developed for hemineglect (Plummer, Morris, & Dunai, 2003). However, despite this, one third of patients suffer from persistent symptoms more than one year after the incident (Kerkhoff & Schenk, 2012). Patients can exhibit an isolated type of hemineglect, or a combination of several hemineglect behaviours (e.g., egocentric, allocentric, auditory, tactile; see Section 1.1.2 for more details). Most of the literature and clinical interest addresses egocentric hemineglect using perceptive measures. As consequence, egocentric hemineglect is largely assessed and rehabilitated. However, there has been less interest payed to disentangle the other forms of hemineglect. This problem is enhanced by the time pressure in clinical routine where therapists have to make a choice between tests (Petzold et al., 2014) and tend to favour tests highlighting the more salient forms of the deficit.

This thesis brings new insights into the evaluation, rehabilitation and understanding of hemineglect through perception and action measures, with the aim to help patients suffering from this condition, as well as clinicians and researchers. In this general introduction, the literature relevant to this thesis will be reviewed. This review will start by describing hemineglect, its heterogeneous manifestations and its different explanatory models. Then the different possible evaluation methods will be presented for the types of hemineglect relevant for this thesis. The following section will report the frequently associated disorders. The most effective conventional rehabilitation techniques of hemineglect will then be reviewed. Finally, the last section will provide a summary of the main objectives of the thesis.

1.1 Hemineglect

1.1.1 Definition

Hemineglect is defined as a difficulty to report or respond to stimuli presented contralateral to a brain lesion, without the cause being explained by elementary sensory or motor deficits such as hemianopia or hemiparesis (Heilman, Valenstein, & Watson, 2000). Hemineglect was first described in a single case report of Jackson and Gowers (1875). They noticed that the case patient had difficulties in reading behaviour, where the patient started reading at the right lower corner and tried to read backwards. They named it “imperception” and suggested a possible lateralisation of the deficit. The term “neglect” was used for the first time by Pineas (1931) when describing a patient without any sensory-motor deficit, but with a complete denial of the left part of body and space. However, Brain’s research formed the pillar conceptualisation of hemineglect (Brain, 1941). He considered the disorder as a neurological condition and suggested a strong association with posterior lesions of the right hemisphere, being dissociate from visual field deficits, topographical memory loss or visual agnosia. Since this period, research on hemineglect has exponentially increased, with the objectives to better understand the condition and the normal cognitive spatial processes (J. Marshall & Robertson, 2013).

Hemineglect mainly occurs following a stroke incident, but signs of hemineglect have been observed in patients with brain tumours, traumatic brain injury, neurodegenerative diseases and demyelinating diseases (Andrade et al., 2010; Butter, Evans, Kirsch, & Kewman, 1989; Gilad, Sadeh, Boaz, & Lampl, 2006; Shinoura et al., 2009). Several studies reported that hemineglect is present in approximately 23% of first stoke acute stage patients (Appelros, Karlsson, Seiger, & Nydevik, 2002; Kamtchum Tatuene et al., 2016). However, estimates of prevalence are difficult to obtain because they depend on different criteria and tests used to establish a sample of patients. Time post-onset is also an important variable in the prevalence estimation. Stone et al. (1991) suggested that three days post stroke showed an equal prevalence of hemineglect following right or left hemisphere damage, whereas three months after stroke, prevalence was greater in right than left brain damaged patients. The difference of prevalence and severity of hemineglect as a function of hemisphere lesion has been confirmed by large cohort studies showing that hemineglect was typically more persistent (indicated by a longer stay at the hospital) and slower to recover for right than left hemisphere stroke lesions (Ringman, Saver, Woolson, Clarke, & Adams, 2004; Stone, Patel, Greenwood, & Halligan, 1992; Ten Brink, Verwer, Biesbroek, Visser-Meily, & Nijboer, 2017). Furthermore, the cortical atrophy tended to be greater in older adults, providing less chance to regain normal (brain-behaviour) functioning (Gottesman et al., 2008; Ringman et al., 2004).

Hemineglect has been reported to prevent functional remission of patients (Gillen, Tennen, & McKee, 2005; Jehkonen et al., 2000; Paolucci et al., 1998). At onset, hemineglect is often characterised by a major deviation of the entire posture, called “pusher syndrome”, where the head, eyes and trunk are oriented towards ipsilateral space (Honore, Saj, Bernati, & Rousseaux, 2009). The condition also significantly hinders daily activities, especially personal grooming, dressing, eating and interactive displacement (Azouvi et al., 1996; Pradat-Diehl & Peskine, 2006; Pradat-Diehl, Poncet, Migeot, & Taillefer, 2010). For example, in an evaluation of daily life deficits using the Catherine Bergego scale (see Section 1.1.4.1), 76% of sixty-nine stroke hemineglect patients showed difficulties on at least one of the ten daily-living activities evaluated, with 36% of the patients exhibiting a moderate to a severe behavioural hemineglect (Azouvi, Samuel, et al., 2002).

To summarize, the hemineglect condition frequently occurs after stroke and symptoms can persist more than one year after the neurologic incident, having a detrimental impact on individual functioning. The next section will describe the different types of hemineglect manifestations.

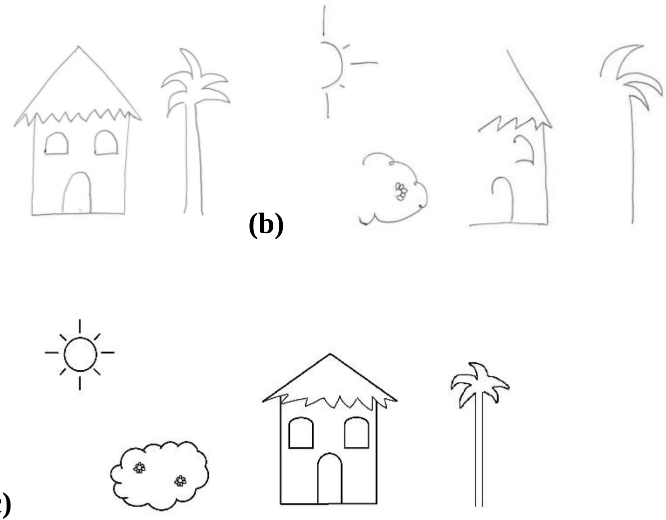
1.1.2 Types

Hemineglect is a heterogeneous condition that disrupts simultaneously or independently different modalities and different frames of reference (Heilman et al., 2000; Plummer et al., 2003).

Hemineglect can influence sensory, motor or representational **modalities**. Sensory hemineglect is defined as an inability to perceive visual, auditory or tactile stimuli on the contralesional side (Plummer et al., 2003). Motor hemineglect consists of a failure in the generation of a movement response to a stimulus that is not caused by a primary motor deficit (Heilman, Bowers, Coslett, Whelan, & Watson, 1985; Laplane & Degos, 1983; Plummer et al., 2003). Representational hemineglect is defined as the failure to report the contralesional half of internally generated spatial scenes (Bisiach & Luzzatti, 1978; Kerkhoff, 2001).

Hemineglect can also depend on the **frame of reference** adopted by the patients. The condition can be body-centred or space-centred (Heilman et al., 2000; Plummer et al., 2003). Patients who fail to explore the contralesional part of their body when grooming or dressing are said to have personal neglect. Spatial hemineglect instead refers to the inability of patients to acknowledge stimuli that are presented in the contralesional hemispace. Two further distinctions exist in spatial hemineglect. Firstly, patients can demonstrate a failure to explore the space that is within reach (i.e., peripersonal space) or the space that is outside of reach (i.e., extrapersonal space). Secondly, patients can neglect half of the space with respect to their viewpoint (i.e., mid-sagittal plane of their body’s trunk, head and eyes), called egocentric or viewer-centred hemineglect (Figure 1a). In contrast, patients can neglect the half side of each stimuli irrespective of their viewpoint, called allocentric or object-centred hemineglect (Figure 1b) (Kerkhoff, 2001; Rorden et al., 2012).

In this thesis, we chose to focus on egocentric and allocentric visuo-spatial hemineglect, and on motor hemineglect. To this aim, the following paragraphs will further detail these types of hemineglect.



(a) **(b)** **(c)**

Figure 1. (a) Illustration of left egocentric hemineglect and (b) left allocentric hemineglect in (c) a copy of drawing.

Several researchers claimed that **allocentric hemineglect** is a sub-type of **egocentric hemineglect** (Driver & Pouget, 2000; Rorden et al., 2012). Following their idea, hemineglect can be distributed either on the stimulus or on space depending on the region of stimuli fixation (or "retinal position"). If the retinal position of a left hemineglect patient is on the right side of a stimulus, the left part of the stimulus will be neglected. Instead, if the retinal position is on the left of the stimulus, it will be perceived entirely (Driver & Pouget, 2000). Other authors supported the same idea by showing that the frame of reference of hemineglect can be modified depending on task instructions (Baylis, Baylis, & Gore, 2004). If the instruction requires to detect a stimulus within an entire monitor, all the contralesional space will be missed. Instead, if the instruction requires to detect a stimulus within a particular object present on the monitor, only the contralesional part of the object will be neglected. In contrast, there are studies providing evidence of double dissociations between egocentric and allocentric hemineglect among stroke patients on tasks requiring a unique instruction in the visual and tactile modalities (Marsh & Hillis, 2008). According to the literature, the incidence of egocentric hemineglect is more frequent than allocentric hemineglect (Marsh & Hillis, 2008). Research reporting that one type of hemineglect can occur independently to another, suggests that egocentric and allocentric hemineglect may reflect damage in different brain areas.

Hemineglect has often been reported as a consequence of a lesion to the inferior parietal lobule (Lunven & Bartolomeo, 2017). However, there is no strong consensus about the anatomical correlates of the condition. Many different results have been reported (e.g., based on focal cortical damage, or disconnection between interconnected areas) possibly because of the heterogeneity of the impairment, and because of different brain imaging techniques (e.g., structural versus functional imaging) (Chechlacz et al., 2010; Karnath & Rorden, 2012; Lunven & Bartolomeo, 2017). For example, studies have investigated hemineglect brain lesions using voxel wise analysis combined with diffusion tensor imaging and behavioural measures from the Apples test (i.e., a single task evaluating both egocentric and allocentric hemineglect, see Section 1.1.4.2) (Chechlacz et al., 2010; Karnath & Rorden, 2012). The results showed that egocentric hemineglect was associated with anterior cortical damage, namely the middle frontal, postcentral, supramarginal and superior temporal gyri, as well as subcortical structures. In contrast, allocentric hemineglect was linked to posterior cortical lesions regions such as the posterior superior temporal sulcus, angular, middle temporal and middle occipital gyri. Additionally, damage to the intraparietal sulcus, the temporo-parietal junction and to the white matter pathways (i.e., superior longitudinal, superior fronto-occipital, inferior longitudinal and inferior fronto-occipital fascicule, thalamic radiation and corona radiate) were responsible for both egocentric and allocentric hemineglect. Similar dissociations have been discovered in other research (Hillis et al., 2005; Medina et al., 2009).

Motor hemineglect has been less investigated than visuo-spatial hemineglect (Sampanis & Riddoch, 2013). The symptoms of motor hemineglect can be diverse, and as consequence, has led to an unclear understanding of this type of hemineglect (Sampanis & Riddoch, 2013). In the literature, motor hemineglect can mainly be distinguished into two types of manifestations (Punt & Riddoch, 2006; Sampanis & Riddoch, 2013).

Firstly, motor hemineglect was described by Laplane and Degos (1983) as an underuse of one side of the body that is not caused by strength, reflex, dexterity or sensitivity deficits. This type of hemineglect is considered as a form of personal neglect affecting the contralesional side of the body. The deficit affects lower and upper extremities, but with a predominance of impairment in the upper limb. Patients behave as if they were hemiplegic, however, the underuse of the limb disappears under verbal encouragement (Laplane & Degos, 1983). This type of hemineglect was characterized by a non- or weak-participation of the contralesional limb in bimanual tasks (e.g., opening a bottle), the absence of hand spontaneous gesturing while speaking, and the absence of arm swing or a lag in leg movement while walking

(Sampanis & Riddoch, 2013). Patients are also described as having a lack of "spontaneous placing reaction", meaning that they will let their arm hang out of the bed or let their leg hang beside the chair (Laplane & Degos, 1983).

The second form of motor hemineglect refers to other motor behaviours often named premotor neglect or intentional motor neglect (Saevarsson, 2013). They are characterized by impaired action kinematics, such as a delayed movement initiation (i.e., directional hypokinesia), a slowness in movement execution (e.g., movement time, peak velocity; i.e., directional bradykinesia), a reduced spatial exploration and amplitude (i.e., directional hypometria), and an inability to sustain an action (i.e., motor impersistence) (Heilman et al., 1985; Kerkhoff, 2001; Sampanis & Riddoch, 2013; Siekierka-Kleiser, Kleiser, Wohlschläger, Freund, & Seitz, 2006). These characteristics are specific to action kinematics towards the contralesional space regardless of the limb used (Mattingley, Phillips, & Bradshaw, 1994). In the continuation of the thesis, this type of hemineglect will be referred to as "spatial motor hemineglect" in contrast to "personal motor hemineglect" described in the previous paragraph. The general term "motor hemineglect" will refer to both types of hemineglect.

Motor hemineglect is more prevalent than commonly believed, especially in patients exhibiting hemiparesis or hemiplegia (Siekierka-Kleiser et al., 2006). Most studies report the prevalence of motor hemineglect without distinguishing the two forms (i.e., spatial motor or personal motor hemineglect). Buxbaum et al. (2004) ran a large cohort study and claimed an incidence of 17% in acute, and of 11% in chronic right stroke patients. Additionally, they reported that 3% of acute and 11% of chronic patients presented both visuo-spatial and motor hemineglect. Other studies have reported similar associations between visuo-spatial and motor hemineglect, as well as dissociations (Buxbaum et al., 2004; Laplane & Degos, 1983).

Laplane and Degos (1983) suggested that personal motor hemineglect is linked to the parietal association areas, secondary motor area, premotor cortex, thalamus and the ventrolateral nucleus, which are areas associated to the preparation or planning of the movement. In accordance to their hypothesis, this deficit could consist in a defect in triggering these areas, where interconnections are essential to maintain their functioning. The study of Classen et al. (1997) favoured the idea that various lesions of cortical and subcortical areas directly or indirectly linked to the primary motor cortex induce a deafferentation and produce an overactivity of the inhibitory interneurons, which then disrupt the activity of pyramidal tract cells involved in the control of motor functions. In response to this finding, Coulthard, Rudd, and Husain (2008) tested the inhibitory process involved in personal motor hemineglect using a masked prime task. Their conclusions confirmed the presence of a deficit to inhibit ipsilesional limb motor plans. They showed that left hemineglect patients failed to inhibit right hand motor plans evoked by the prime, disrupting left hand action planning of movement initiation. This lateralised inhibitory deficit was mainly observed in patients with lesions to the putamen and enclosing white matter, which are areas closely linked to motor association and medial prefrontal regions.

Concerning spatial motor hemineglect, a review suggested that directional hypokinesia and bradykinesia correspond to deficits in the visuo-motor control system, involving the parietal and frontal cortex, the white matter connecting the two areas and subcortical regions (Coulthard, Parton, & Husain, 2006). Another recent review suggested that frontal, parietal and subcortical lesions are more related to spatial motor hemineglect than personal motor hemineglect (Saevarsson, 2013). Also, Sapir, Kaplan, He, and Corbetta (2007) conducted an anatomical analysis on patients exhibiting directional hypokinesia, suggesting that the impairment is consecutive to lesions in the ventral lateral putamen, the claustrum and the white matter below the frontal lobe in front of the central sulcus.

To summarize, the term "hemineglect" can refer to a large spectrum of manifestations. To this aim, different designations have been used to explain the different types of deficit. In the context of this thesis, we focus on visuo-spatial egocentric and allocentric forms, as well as on the motor form of hemineglect, particularly the action kinematic impairments in spatial motor hemineglect. Note that the motor type is less investigated and less well understood than the visuo-spatial hemineglect type. No strong neuroanatomical consensus has been established concerning hemineglect, but overlapping networks among different types of hemineglect have been highlighted. In the next section, different models of hemineglect will be reviewed.

1.1.3 Models

Several theories and models have been created to provide a possible explanation of the contralesional bias exhibited by patients with hemineglect. Nevertheless, given the heterogeneity of the impairment, none of the models successfully explain the entire disorder (Ting et al., 2011). Rather, each model can account for some features of hemineglect (Kerkhoff, 2001). Some of the models most related to this thesis will be briefly presented.

Hemineglect can be explained by a disruption of attention. Attention is described as the selection of the most important incoming stimuli in the face of limited cognitive processing capacity (Heilman et al., 2000). Spatial attention is the ability to direct attention to a specific location in space (Chechlacz, Humphreys, & Cazzoli, 2016). In the behaviour of hemineglect, patients demonstrate an impairment to allocate attention to the contralesional side of space. Different models explain the cognitive processes that may allow allocation of attention in space.

Heilman, Bowers, Valenstein, and Watson (1993) presented an attentional model. In addition to the limited capacity to process information, their model suggested that the brain has a limited capacity for preparing action. Action selection is made by an intentional cognitive process with a spatial dimension (Heilman et al., 2000), where deficits in producing movements towards the contralesional space are causing directional hypokinesia or bradykinesia. In this model, Heilman and colleagues suggested that the attentional circuit relies on the thalamus to select information before sending it to the cortex and associative areas, while the intentional process relies on two circuits coming either from the supplementary motor area or the prefrontal area (and implicating the thalamus and basal nuclei) (Azouvi, Samuel, & Louis-Dreyfus, 2000a). This model proposed that the right hemisphere is dominant and controls orientation of attention towards both hemispaces, while the left hemisphere can only direct attention towards the contralateral hemispace. They proposed that lesions in the right hemisphere will therefore lead to a left hemineglect impairment since the left hemisphere cannot compensate for the deficit in orienting attention towards the left hemifield. However, a lesion to the left hemisphere is less likely to produce a right hemineglect since the right hemisphere remains intact to orient attention towards the right hemispace. They suggested that this explanation could be the reason for the higher prevalence of left hemineglect patients.

Kinsbourne (1993) also established an attentional model providing an explanation for the higher prevalence of left hemineglect. This model proposed a mutual inhibition of both hemispheres through vectors. The attentional vector of the left hemisphere was stronger than the one of the right hemisphere. Therefore, a lesion of the right hemisphere would lead to a reduced inhibition on the left hemisphere, making it stronger and hyper-attentive to right hemispace, thereby creating left hemineglect. However, the model proposed that a left brain lesion deficit would re-equilibrate the intensity of inhibition between both hemispheres, and not (or poorly) lead to hemineglect symptoms (Urbanski et al., 2007). This model received support from different experimental studies such as Koch et al. (2008). These authors demonstrated that the application of inhibitory repetitive Transcranial Magnetic Stimulation (rTMS; low frequency 1Hz) on the left posterior parietal cortex of right brain damaged patients improved visual hemineglect by reducing the hemispheric imbalance by attenuating the over-excitability of the left hemisphere.

A third influential attentional model of hemineglect was provided by Posner and Petersen (1990). This model suggested that spatial orientation can be either an automatic (exogenous attention) or a voluntary (endogenous attention) process, and can be separated in three steps: (i) alertness; (ii) disengagement from the current focus; and (iii) engagement of attention on a novel target (Urbanski et al., 2007). Disengagement relies on the superior colliculus whereas the engagement depends on the pulvinar. According to this model, hemineglect could be explained by a deficit in exogenous attention specifically in the disengagement phase. Hemineglect patients exhibit difficulties to reorient attention towards the contralesional hemispace since they have difficulties to disengage attention from ipsilesional targets (Bartolomeo & Chokron, 2002; Kerkhoff, 2001).

The model of Rizzolatti, Fadiga, Fogassi, and Gallese (1997) provided a combined attentional and representational explanation of hemineglect. This model claimed that space representation is motorically constructed by actions in different portions of space. They proposed that it is the activity of the premotor cortical areas that shape the representation of space, and in turn influence attention. They suggested that lesions to specific premotor areas lead to a deficit in the neural representation of a specific portion of space, and correspond to the presence of hemineglect in a particular space sector (Kerkhoff, 2001). This model can be used to account for both attentional and motor hemineglect (Punt & Riddoch, 2006).

The spatial remapping model of Pisella and Mattingley (2004) provided a complementary explanation to attentional models and to the understanding of visuo-spatial hemineglect. This model suggested the presence of a retinotopic/oculocentric salience map in the parietal cortex that codes the salience of each visual stimuli in the visual field, and determines which stimuli are salient enough to be processed at the level of conscious perception. The model also proposed the presence of a remapping system that maintains stable and spatially relevant visual stimuli on the salience map across ocular saccades and attentional shifts. According to this model, the salience map of patients with right parietal damage is biased, causing left hemineglect. The salience associated to the same visual stimulus changes depending on its position in the visual field, with relatively little salience and minimal attentional weight for a visual stimulus in the contralesional visual field. Moreover, hemineglect patients present an impairment of the remapping mechanism, which leads to distortions or loss of visual awareness for encoded elements in a part of the visual field. In the case of a right posterior parietal lobe lesion and following a leftward saccade, the entire salience map is overwritten. However, a rightward saccade overwrites the left visual field of the previous fixation position in the salience map. In the case of a left posterior parietal lobe lesion, it is the salience map of the visual field opposite to the direction of the saccade that is overwritten. In this sense, patients with a left lesion are able to explore the whole visual field from left to right and vice-versa. However, when patients with a right lesion make a left saccade, either they stop their exploration, or they are attracted back by an ipsilesional stimuli that is more salient, thereby leading to left hemineglect.

To summarize, currently no single model can reflect the heterogeneity of hemineglect symptoms. Several theories have been reported, mainly explaining visuo-spatial hemineglect, but some including motor hemineglect. Most theories describe hemineglect as a consequence of an attentional disruption. In the next section, the evaluation of hemineglect will be reviewed.

1.1.4 Evaluation

The evaluation of hemineglect has crucial importance for recovery since it orients the clinician in the selection of appropriate therapies. Given that hemineglect is a multi-modal and multi-faceted impairment, rigorous and quantitative evaluations are needed in order to precisely define the type and severity of hemineglect exhibited by a patient. It is therefore necessary to administer several assessments to obtain a comprehensive diagnosis (Bailey, Riddoch, & Crome, 2000). It has to be noted that the inherent characteristics of the tests (e.g., target/distractor ratio and similarity) influence their sensitivity, and can lead to apparent double dissociations for the same patient between two tests assessing the same type of hemineglect (Bailey et al., 2000; Basagni et al., 2017). The therapist should therefore establish a relevant and wide combination of different assessments and interpret them carefully in parallel to considering clinical observations. Unfortunately, due to time pressure in clinical routine, the therapist often has to make a selection between different possible tests (Petzold et al., 2014). Since patients exhibiting hemineglect frequently have concurrent contralesional hemiparesis, testing has mainly been performed with the ipsilesional hand (Ogourtsova, Archambault, & Lamontagne, 2015). In the following sections, the different assessments of hemineglect will be reviewed, focussing on tests for egocentric, allocentric and motor hemineglect.

1.1.4.1 Egocentric hemineglect

Egocentric hemineglect is the most investigated type of hemineglect. The clinical evaluation of egocentric hemineglect can be made using various assessments that typically involve the patient being sat in front of the experimenter, and the test presented in front of their body midline. The tests can be classified into four categories: visuo-perceptive, visuo-graphic, computerised and behavioural. Here, we review the most common tests in the literature and the more recent innovative assessments.

The **visuo-perceptive tests** require that patients provide a perceptual response. For example, the overlapping figures test consists in presenting five overlapping figures of common objects (i.e., two figures that overlap on the right, two that overlap on the left, and one in the centre overlapping with all the others). The patients are asked to recognize each figure by pointing to the same figure drawn separately on a multiple choice board that also contains distractors (Gainotti, D'Erme, Monteleone, & Silveri, 1986). Patients are diagnosed with hemineglect if they make a double of omissions on the contralesional side in comparison to the ipsilesional side. Reading tests are also used to diagnose lateralised perceptual impairments. They vary depending on the language of the patient, but the instructions are similar. The patients read text or isolated words, and the experimenter counts the number of word or letter omissions. For the French speakers, the text “le vernis à ongles” is the most frequently used, with a cut-off score of two omissions indicating hemineglect (Azouvi, Bartolomeo, et al., 2002).

The **visuo-graphic tests** require that patients perform a perceptive task by giving a graphical response. These tests are typically paper and pencil tests. The cancellation tests are the most used because they are easy to administer and to quantify (Bowen, McKenna, & Tallis, 1999). Patients have to cross out or circle targets that are presented on a horizontal sheet of paper and ignore distractors. Patients exhibiting hemineglect have the tendency to omit targets that are located on the contralesional side of the test, which creates an asymmetry of omissions in comparison to the ipsilesional side. Additionally, these tests allow to observe the scanning pattern of patients (Azouvi, Samuel, et al., 2002). In all cancellation tests, number of targets and distractors are evenly distributed on the right and left sides of the sheet of paper. Moreover, some tests distribute targets and distractors equally in columns (and rows) (e.g., the Bells test). Numerous versions of cancellation tests have been developed, including letters, lines, stars, bells and apples cancellation (Azouvi et al., 2000a). It has been shown that cancellation tests that increase attentional load by including distractors are more sensitive to detect hemineglect (Gauthier, Dehaut, & Joanette, 1989; Kaplan et al., 1991; Vanier et al., 1990). The sensitivity of the cancellation tests can also be influenced by similarities between target and distractors, the target/distractor ratio, the density of stimuli and the addition of a demanding secondary task (Basagni et al., 2017; Robertson & Frasca, 1991). Over the years, the Bells test (Gauthier et al., 1989) has been one of the most studied and most sensitive cancellation test (Basagni et al., 2017; Oliveira de CR, Luara de FC, Karina, & Rochele, 2016; Vanier et al., 1990). The test requires that the patient circles, as quickly as possible, 35 bells presented among 280 distractors placed equally in a structured array of seven columns (i.e., three left, three right and one central). Targets and distractors have the same colour and the same size. The starting position, total number of omissions, omissions' asymmetry (i.e., left omissions minus right omissions), and total time is compared to norms in order to diagnose whether or not a patient has egocentric hemineglect.

The line bisection tests consists in the patient estimating, as precisely as possible, the middle of different lines presented on a sheet of paper (Schenkenberg, Bradford, & Ajax, 1980). These tests are scored by measuring the deviation of response in comparison to the true centre of the line. Patients presenting hemineglect displace the middle of the line towards their ipsilesional side, and this effect can be magnified when the lines are long or placed in the contralesional hemispace (Azouvi et al., 2000a). Surprisingly, when the lines are short, the lateral bias can be towards the ipsilesional side (Halligan & Marshall, 1988). Recently, a new method for administering and analysing line bisection was proposed (McIntosh, Ietswaart, & Milner, 2017; McIntosh, Schindler, Birchall, & Milner, 2005). The method consists in placing the lines in different positions relative to the centre of a sheet of paper.

For example, in a basic version of the test, four horizontal lines are individually presented on four sheets of paper. On one page, a 16cm line is positioned in the centre (from -80 to +80mm). Similarly, on a second page, an 8cm line (from -40 to +40mm) is presented. For these two stimuli, the midpoint of the lines is the centre of the page. For the other two pages, 12cm lines are presented, one on the left side of the page and one on the right side of the page (from -80 to +40mm and from -40 to +80mm respectively). This means that across the trials, the left endpoint of the line could be at a different position while keeping the right endpoint of the line at the same position (e.g., a line can be placed from -40 to +80 and another one from -80 to +80) and vice-versa. The method allows to measure shifts in patient's responses (named 'weighting') relative to the position of the line on the page and the change in line endpoint. For example, the "left endpoint weighting" corresponds to the average shift in the patient's responses for the different left line endpoints (e.g., lines from -40 to +80 and from -80 to +80). The subtraction of the 'left endpoint weighting' from the 'right endpoint weighting' provides a measure of hemineglect asymmetry. A total weighting measure (i.e., the sum of the patient's 'right and left endpoint weightings') can also be calculated to obtain a non-lateralised measure of overall attention allocation. This new measurement has been demonstrated to be more sensitive than the standard line bisection measure, whereby patients with hemineglect are mainly affected by a change of the line endpoint in the ipsilesional hemifield (McIntosh et al., 2017; McIntosh et al., 2005).

Drawing and copying tests are also methods to evaluate hemineglect. Patients are typically asked to draw a figure from memory or to copy an image (Ogden, 1985). An asymmetric drawing with an absence of the contralesional part, or a transposition of elements presented on the contralesional part to the ipsilesional part, or exclusive use of the ipsilesional part of the sheet of paper, can all be used to identify hemineglect (Ting et al., 2011). However, several studies do not recommend the use of drawing tests in hemineglect diagnosis because of the lack of sensitivity, the important influence of subjectivity and the impact of other potential cognitive impairments (e.g., apraxia) that can confound the measure (Bailey et al., 2000; Plummer et al., 2003).

It should be noted that for some authors the use of visuo-graphics tests and their scoring system do not always allow to clearly distinguish visuo-spatial egocentric from spatial motor hemineglect (Plummer et al., 2003). Contralesional omissions on cancellation tests or ipsilesional shifts in line bisection tests could be explained by a failure to orient attention to the contralesional hemifield (Heilman et al., 2000) or as a motor deficit preventing normal and complete movement towards the contralesional hemispace (Heilman et al., 1985; Laplane & Degos, 1983). This point will be further detailed in the section about motor hemineglect evaluation (see Section 1.1.4.3).

Computerised tests are recommended to allow for a more sensitive and specific evaluation of hemineglect. They provide measures of reaction time and are less influenced by learning effects (Bonato, 2012; Erez, Katz, Ring, & Soroker, 2009). Recently, researchers begin to transpose paper and pencil tests into computerised tests. Fordell, Bodin, Bucht, and Malm (2011) created a computerised battery (i.e., VR-DiSTRO) transposing four existing tests: the star cancellation test, the line bisection test, a visual extinction test and the baking tray test (i.e., a behavioural test explained further in this section). Their aim was to develop an intuitive easy-to-use device to assess hemineglect with a higher accuracy caused by tracking the scanning pattern made by the patient. This battery was validated against existing tests and the total sensitivity and specificity of the battery was high (respectively 100% and 82%), but the separate sensitivity of the line bisection and the star cancellation was low to moderate (respectively 33% and 54%). Tanaka, Ifukube, Sugihara, and Izumi (2010) explored different versions of the line cancellation tests (e.g., object-centred, viewer-centred) with a head mounted display. Results on two patients demonstrated that the tool can be useful to more precisely define the area that is neglected, but they suggested that additional eyes, head and trunk trackers would be needed to increase the precision of the measure.

Different computerised tests also exist independently of validated paper and pencil tests. For example, the Test for Attentional Performance (TAP) is a computerised battery that includes thirteen tests that assess several attentional functions (Zimmermann & Fimm, 1995). One of the subtests of this battery is specific for the evaluation of hemineglect; the “Neglect” subtest. This test displays white distractors (i.e., numbers), on a black background, equally placed in four quadrants forming a square. The target (i.e., a blinking increasing number) appears at random intervals among the distractors at different places across the screen. Patients are required to fixate the centre of the screen and press a response button as quickly as possible when they detect the presence of the target. Reaction time and omissions relative to target position are recorded and used to diagnose hemineglect.

In addition to the performance at the clinical tests, it is important to always consider the **behaviour** of patients. In fact, patients can show no signs of hemineglect on the tests, but bump into the door just after finishing the neuropsychological assessment (Ten Brink, 2018). This discrepancy between clinical measures and everyday life behaviour has been mostly observed in chronic patients. It can be explained by the learning of compensatory strategies for tests (i.e., retest effect) or by differences in underlying mechanisms. Standardised tests may require voluntary attention, whereas daily life situations are much more complex, and may rely more on automatic orientation of attention (Azouvi, 2017). Also, classical tests concern mainly peripersonal space, whereas in daily living, personal, peripersonal and extrapersonal spaces all have a major importance (Ten Brink, 2018). An ecological assessment is therefore needed for better evaluation of hemineglect.

Different scales have been developed to evaluate ecological situations. The Catherine Bergego Scale was created to evaluate hemineglect behaviour through observation of the patient in ten everyday life situations with a semi-quantitative questionnaire (e.g., forgot to wipe the left side of his mouth after eating) (Bergego et al., 1995). For each item, the therapist or the relative scores behaviours from 0 (absence of hemineglect) to 3 (severe hemineglect). A total score from 1 to 10 indicates a mild hemineglect, from 11 to 20 a moderate hemineglect and from 21 to 30 a severe hemineglect. Additionally, an auto-evaluation of the questionnaire exists in order to compare observations with auto-reported difficulties and assess the anosognosia of the patient (see Section 1.1.5). Anosognosia is calculated from the difference between the examiner and patient ratings. Different studies have demonstrated a good internal consistency and sensitivity (Azouvi et al., 1996; Azouvi et al., 2003). Towle and Lincoln (1991) developed a similar questionnaire relying on daily observations that also demonstrated good internal properties and correlations with performance on the star cancellation test (Azouvi, 2017).

Other authors have favoured the development of tests which simulate daily living activities. The baking tray task for example consists of placing sixteen cubes as evenly as possible across a board as if they were buns on a tray that were to be put into an oven (Tham, 1996). When the task was finished (no time limit), the numbers of cubes in each half of space was counted. The sensitivity of the test has been demonstrated against other behavioural tests (Appelros, Karlsson, Thorwalls, Tham, & Nydervik, 2004). The assessment of Eschenbeck et al. (2010) goes further in ecological measures by asking patients to actually perform activities of daily living such as dialling a phone number, filling out a form or counting money. Patients were diagnosed as having hemineglect if they failed at least one of the daily living tasks. High inter-rater reliability, and significant association between the daily activities assessment and classical paper and pencil tests were demonstrated.

More recently, new tools have been created to assess everyday life behaviour in more complex and potentially dangerous situations. Several studies have been using Virtual Reality (VR), a technology that enables the user to interact and engage in a simulated environment that appears identical to the real world (Weiss & Jessel, 1998). The VR-system includes multimedia peripherals and sensors that offer the possibility to manipulate and perform actions in a safe and ecological environment. Moreover, it increases the standardisation of the assessment and provides objective measures (Weiss, Kizony, Feintuch, & Katz, 2006). The VR-system can be immersive, where the patient is completely isolated from the real world by wearing a head-mounted display that provides a first-person perspective. The VR-system can also be non-immersive, where the patient is represented on a screen by an avatar within the virtual environment, and the interaction is made through the use of a mouse or a joystick (Ogourtsova, Souza Silva, Archambault, & Lamontagne, 2015).

Myers and Bierig (2000) have developed a three-room virtual house with a backyard for the assessment of hemineglect within a head-mounted display. While the patient scans the virtual environment, the maximal angle of head rotation (to the left versus to the right), the time to reach the maximal angle and the number of cues needed to turn the head towards the contralesional field was recorded. Preliminary results suggested that the tool can provide a potential diagnosis measure of hemineglect. However, its validity and sensitivity have still to be tested. Another group of researchers created a virtual town in order to assess hemineglect (Peskine et al., 2011). Patients were equipped with a head-mounted display, sat on a swivel chair and they were asked to orientate themselves in the virtual world using a mouse. The task consisted in detecting swings in a park, as well as counting the number of bus stops along a route. The number of bus stops omitted and their location (left or right regarding patients' orientation) were measured. Results on a small sample of patients showed that the system was able to detect differences between hemineglect patients and controls on total number of omissions and on the relative left to right number of omissions. In a similar task, Buxbaum, Dawson, and Linsley (2012) asked patients to travel along a virtual path, either actively using a joystick and regulating their speed, or passively viewing the scene while the speed was kept constant. While travelling, patients were instructed to report objects presented on both sides of the path and avoid collisions with objects. Travelling along the path included three levels of difficulty. At the first level, twenty objects were presented, ten on the left and ten on the right side of the path (trees, statues and animals). The second level included twenty more objects that served as distractors, such as fountains and benches. At the third level, in addition to the forty objects, auditory and visual distractors were added. Patients had to perform each level twice, in the two directions along the same path. The VR-system was tested on a large cohort of patients and results demonstrated good sensitivity and specificity, minimal practice effect, and strong validity in comparison to classical paper and pencil tests. Maintaining the idea of ecological tests, other groups of researchers have established virtual street-crossing tasks. For example, D. Kim et al. (2010) created a test where the patient was represented by an avatar in the middle of a pedestrian crossing. Patients were instructed to scan both sides of the street and push the mouse button in order to stop the cars coming towards the avatar. As a car approached an avatar, the headlights were turned on as a visual cue to help patients detect the car and react adequately. If patients did not react after the visual cue, an alarm (auditory) cue was activated. The trial ended if the patient did not react after two cues. This ecological street crossing system demonstrated to be reliable for diagnosing hemineglect.

To summarize, a large number of egocentric assessments have been developed. Since the detection of hemineglect can depend on the type of administered assessments, it is recommended to combine tests from different categories, favouring computerised and technological tests, which have shown to be more sensitive than standard paper and pencil tests. Additionally, it is worth noting that high attentional load (e.g., presence of distractors) increases the sensitivity of tests, allowing better chances for detecting subtle hemineglect impairments. In the next section, allocentric hemineglect evaluation will be reviewed.

1.1.4.2 Allocentric hemineglect

Allocentric hemineglect is evaluated relatively less frequently than egocentric hemineglect. One of the first attempts to evaluate allocentric hemineglect consisted in asking patients to take photographs of lines or objects so that the lines or objects would appear in the centre of the picture. The evaluation consisted in judging whether the object was centred in the middle of the photograph or to one side (Chatterjee, 1994). If the line or object was located towards the ipsilesional side of the photograph, it was proposed that the bias referred to an egocentric hemineglect profile. Instead if located to the contralesional side, it was proposed that the error indicated the presence of allocentric hemineglect. Since this first test, a few clinical tests have been developed for measuring allocentric hemineglect more precisely. These tests are similar to egocentric tests, but the dependent variables used to quantify the impairment are not the same. The tests can be classified in visuo-perceptive and visuo-graphic categories.

Reading tests form part of the **visuo-perceptive category**. The instructions are the same as for the egocentric evaluation. However, instead of counting the number of words omitted on the contralesional hemispace, allocentric hemineglect is reflected by errors on contralesional side of words (e.g., mouse → house) (Haywood & Coltheart, 2000).

Concerning **visuo-graphic tests**, memory or copying of drawings are commonly used (Rode & Pisella, 2011). Allocentric hemineglect can be demonstrated by an absence of drawing of the contralesional side of an object. For example, in the Ogden scene (Ogden, 1985), allocentric left hemineglect patients typically omit to draw the left part of the house, but without omitting the presence of the tree situated in the left hemispace of the scene. Line bisection tests also provide suitable evaluations of the deficit (Schenkenberg et al., 1980). An ipsilesional bias when bisecting the line into two subjective parts can be indicative of an allocentric profile. However, the interpretation of ipsilesional bias on lines centred in the middle of the sheet of paper can be confused with egocentric hemineglect. Therefore, it is more straightforward to use line bisection tests where lines are distributed across the page without centred lines.

Some cancellation tests have been developed for the combined evaluation of egocentric and allocentric hemineglect. Ota, Fujii, Suzuki, Fukatsu, and Yamadori (2001) presented a page with circles or triangles, with half of them having a gap in one side (i.e., left or right side of the stimulus). The circles with a missing part looked like a C or a reverse C, whereas the triangles (some inverted) had one of their apex missing to look like an isosceles trapezoid as cut end was closed. Stimuli were drawn randomly on a sheet of paper, but evenly distributed on the left and right part of the page. Patients were required to circle the complete stimuli and cross out the incomplete stimuli. As for classical cancellation tests, omitting to circle or to cross out stimuli on the contralesional hemispace referred to egocentric hemineglect. Instead, circling incorrectly stimuli having a contralesional gap on either part of the space referred to allocentric hemineglect. Based on this first combined cancellation test, another group of researchers improved and validated the Apples test (Bickerton, Samson, Williamson, & Humphreys, 2011). In this test, patients were asked to respond to complete apple stimuli, without making a response to the distractor apples containing a missing part either on the left or right. The aim of this change in instruction was to discourage them from exploring all parts of space, and to make the test closer to classical cancellation tests instructions. The number of stimuli was increased in order to enhance the difficulty and the sensitivity of the test (150 stimuli versus 60 in the test of Ota and colleagues). All stimuli were organised evenly in an invisible grid of five columns and two rows. Asymmetry in target omissions between the two left and two right columns indicated egocentric hemineglect, whereas allocentric hemineglect was defined by the asymmetry in false positive errors (i.e., crossing out an apple with a gap) between the apples with a left or a right gap.

To summarize, few clinical tests assessing allocentric hemineglect exist, all of them addressing allocentric jointly to egocentric hemineglect. In the next section, motor hemineglect diagnosis will be discussed.

1.1.4.3 Motor hemineglect

Despite the considerable number of experimental articles that have attempted to define motor hemineglect, its evaluation remains challenging. Indeed, pure forms of spatial and personal motor hemineglect are rare. Moreover, it is complicated to differentiate personal motor hemineglect from hemiparesis (see Section 1.1.5) as the symptoms and damaged anatomical regions are similar (e.g., more common and severe after a right than left brain lesion) (Classen et al., 1997; Rode, Perenin, Honore, & Boisson, 1998). In addition, as mentioned previously (see Section 1.1.4.1), depending upon the task used (e.g., cancellation tests), it is difficult to clearly distinguish spatial motor hemineglect from visuo-spatial hemineglect (Coulthard et al., 2006; Plummer et al., 2003). Motor hemineglect is therefore not clearly understood and, to our knowledge, no standardised clinical test has been validated for its evaluation in daily clinical routine (Punt & Riddoch, 2006; Saevarsson, 2013). In this section, experimental designs assessing personal and spatial motor hemineglect will be presented. Given the relevance of action kinematics in this thesis, spatial motor hemineglect will be described in more details than personal motor hemineglect.

Personal motor hemineglect can be diagnosed if patients typically act by using their ipsilesional rather than contralesional limb, but are able to move the contralesional limb when given strong verbal incitation or painful stimuli (Laplane & Degos, 1983; Siekierka-Kleiser et al., 2006). Other authors suggested to evaluate personal motor hemineglect using a quantitative motor extinction task (Punt & Riddoch, 2006; Punt, Riddoch, & Humphreys, 2013). Extinction phenomenon is usually tested in the visual modality. It refers to the inability to detect a stimulus located in the contralesional hemifield if another stimulus is simultaneously presented in the ipsilesional hemifield. However, if the contralesional stimulus is presented in isolation, the patient can then detect it (i.e., the presentation of bilateral stimuli impairs performance) (Hillis et al., 2006; Kerkhoff & Schenk, 2012). A motor version comprising two electronic "tappers" was developed (Punt & Riddoch, 2006). Patients were requested to make as many tapping movements as possible for ten seconds following an onset of a signal, using either their contralesional, or ipsilesional index fingers, or both together. If patients showed a disproportionally lower number of taps with their contralesional finger in the bimanual compared to unimanual condition, it would suggest the presence of personal motor hemineglect.

The evaluation of action kinematics in **spatial motor hemineglect** must consider the different steps of goal-directed reach movements. Getting the hand to a target requires the execution of several interacting processes. The first step in visuo-motor control is the selection of the target (Coulthard et al., 2006). Target selection can be modulated either by visual salience (i.e., bottom-up process) (Constantinidis & Steinmetz, 2001) or by intentional goals and expectations (i.e., top-down process) (Platt & Glimcher, 1999). Once the target is selected, the individual then needs to localize the object in eye-centred or effector-centred coordinates. The localisation of the target leads to the creation of a motor command that considers target and effector positions and possible motor error. The kinematics of the reach movement (e.g., speed, peak speed) will be influenced by the target's characteristics and the goal of the movement (e.g., reach a cup of tea depends on the volume of liquid while drinking tea depends on the temperature). Prior to the motor command execution, predictions about the consequences of the movement (i.e., "forward models" of the motor system) are computed. Finally, the reaching movement is executed with the help of visual and somatosensory feedback signals allowing for potential on-line adjustments (Coulthard et al., 2006).

Delayed movement initiation (i.e., directional hypokinesia; reaction time) and slowness in movement execution (i.e., directional bradykinesia; execution time, peak speed, etc.) towards contralesional hemispace, are the action kinematics mostly investigated in experimental designs assessing spatial motor hemineglect. Most of the studies investigating directional hypokinesia used experimental paradigms that attempted to distinguish the condition from visuo-spatial hemineglect. Directional hypokinesia was firstly evaluated using a wooden handle moving on a horizontal metal track (Heilman et al., 1985). Patients were instructed to move the handle as quickly as possible along a fixed linear pathway following the onset of a tone. The apparatus was located either on the right (i.e., the left part of the apparatus was aligned with the patient's body midline) or on the left hemispace. The starting point of the handle was either on the right or left side of the apparatus. Trials were performed with the ipsilesional hand. Presence of directional hypokinesia was suggested when the reaction time (i.e., time between tone onset and the initiation of movement) was slower for movements going towards the contralesional side. The authors claimed that this latter behaviour could indeed be considered as directional hypokinesia because movements were performed with the ipsilesional hand and therefore exempt of hemiplegia. Moreover, the task did not require detection of visual stimuli, excluding the potential influence of visuo-spatial hemineglect.

For assessing directional hypokinesia, some studies developed paradigms dissociating target location in space from the direction of reach. For example, a group of researchers developed a design where patients were instructed to reach to a LED on a horizontal apparatus using their ipsilesional hand (Husain, Mattingley, Rorden, Kennard, & Driver, 2000). The LED could be situated either in their ipsilesional or contralesional hemispace. The starting position was either located in the centre, in the contralesional hemispace (in a further contralesional position than the LED) or in the ipsilesional hemispace (in a further ipsilesional position than the LED). The LED situated in the contralesional hemispace required a contralesional movement when the starting point was located in the centre, while an ipsilesional movement was needed when the starting point was in the contralesional hemispace. Visuo-spatial hemineglect was suggested when a contralesional target was perceived more slowly than an ipsilesional target, regardless of starting position. Additionally, directional hypokinesia was defined as when the initiation time was slower for a contralesional target (central starting point) but improved significantly for the same target when the starting point was situated in the contralesional hemispace. Another group of researchers developed a similar paradigm using two tasks (Bartolomeo, Chokron, & Gainotti, 2001; Bartolomeo, D'Erme, Perri, & Gainotti, 1998). A perceptual task required the patient to detect lateralised stimuli by giving a central response, and a motor task consisted in giving lateralised responses to central stimuli. In the perceptual task, three black circles were displayed horizontally on a computer monitor. Patients were instructed to fixate the central circle and press the central space bar as soon as one of the lateralised circles (i.e., left or right) became grey. In the motor task, three circles were displayed vertically, and patients were required to press right keys on the keyboard when the upper circle became grey, or to press left keys when the lower circle became grey, or to press central keys when the central target became grey. The ipsilesional hand response time (i.e., from target onset to key press) was recorded for both tasks. This paradigm defined a slowness to detect a contralesional target at the perceptual task as visuo-spatial hemineglect, whereas a slowness in contralesional movement at the motor task referred to directional hypokinesia.

Other authors have proposed to assess directional hypokinesia using paper and pencil tests and mirroring effects (Nico, 1996; Tegnér & Levander, 1991). Patients were instructed to perform a line and figure cancellation test under three conditions: (a) normal-view: on a sheet of paper on a table; (b) mirror view: using a 90° angle mirror, where both the sheet of paper and the mirror were aligned to the body midline of the patient, and the direct view was hidden using a wooden bench, and; (c) projected-view: with the use of an overhead projector displaying the stimuli on the opposite wall, and the direct view hidden using a curtain. A greater number of omissions in the patient's contralesional subjective viewpoint (i.e., mirror-view or projected view) would suggest visuo-spatial hemineglect, whereas a greater number of omissions in the patient's ipsilesional subjective viewpoint (i.e., mirror-view or projected view) would suggest a directional hypokinesia (see Coslett, Bowers, Fitzpatrick, Haws, & Heilman, 1990, for similar results). We note that in these studies, the authors ignored the original definition of directional hypokinesia, and rather suggest that omissions and not a delay of reaction time indicated directional hypokinesia. Moreover, these experimental designs used lateralised visual feedback that can complicate the interpretation of results (e.g., in case where the patient mentally rotates their visual representation in accordance to the mirror effect) (Bartolomeo et al., 1998).

Directional bradykinesia was demonstrated for the first time in a study where patients had to perform leftward and rightward sequential movements with the ipsilesional hand on a horizontal response board with LED buttons (Mattingley, Bradshaw, & Phillips, 1992). Each of the buttons was illuminated in turn, so that when a button was released, the next button of the sequence was illuminated. The starting and ending positions were fixed and either situated on the left or right side of space. The authors recorded the time spent in motion between target buttons. Slower movements towards the contralesional side of the board in comparison to the ipsilesional side indicated directional bradykinesia. The same group further tested this impairment (Mattingley et al., 1994). Targets consisting of seven circles of two different diameters were placed vertically in two columns (four targets on one side and three targets on the other side). Patients were instructed to produce a continuous series of six strokes moving a pen to each target and completing three rightward and three leftward strokes. This paradigm allowed to demonstrate directional bradykinesia for movements towards contralesional relative to ipsilesional hemispace on action kinematics of execution time, time to peak, time from peak and jerkiness.

Despite the finding that some paradigms showed the presence of directional bradykinesia, other studies failed to report this impairment (Heilman et al., 1985; Himmelbach & Karnath, 2003; Husain et al., 2000; Konczak & Karnath, 1998;

Mattingley et al., 1998). Indeed, these studies focused on immediate visually guided movements (i.e., on-line movements in opposition to delayed/memory-guided movements), and demonstrated abnormalities in execution, but without being especially directed toward the contralesional space. Those studies supported the existence of general bradykinesia, but not specific to the hemineglect profile (Coulthard et al., 2006; Ogourtsova, Archambault, et al., 2015). Different reasons could explain the discrepancy in results. Firstly, the experimental paradigm and task demand can be highly variable. For example, performing a pointing or a reaching task at eye-level with the head fixated or below eye-level looking at a table leads to different biomechanical movements and different aspects of visual feedback (Coulthard et al., 2006). Secondly, the location of the lesion is essential in defining the consecutive action problems. However, the location of damage varies considerably between studies (Ogourtsova, Archambault, et al., 2015).

To summarize, personal motor hemineglect can be evaluated by observing the use of the contralesional limb, particularly in bimanual tasks. Spatial motor hemineglect can be evaluated using different experimental paradigms that measure action kinematics towards the contralesional hemispace. More interest has been paid to movement initiation and movement execution kinematics. Despite that it is well established that action kinematic abnormalities of the ipsilesional upper limb exist in hemineglect patients, the presence of lateralized deficits towards contralesional hemispace is still debated. Definitions, lesion locations and methodological divergences prevent from a consistent understanding of the disorder, which probably limits the development of standardised assessments for clinical settings. In the next section, the disorders associated with hemineglect will be described.

1.1.5 Associated disorders

Anosognosia, visual field defects and hemiparesis/hemiplegia are commonly associated disorders of hemineglect (Appelros et al., 2002; Kerkhoff, 2001). The first two associated disorders will be briefly reviewed, followed by a detailed review of hemiparesis/hemiplegia because of its essential role in this thesis.

Anosognosia and hemineglect are frequently associated, especially following right hemispheric damage in the parieto-temporo-occipital area (Appelros et al., 2002). The term anosognosia refers to a lack of awareness of sensory, motor or cognitive deficits. Anosognosia can manifest differently within an individual patient. For example, patients can express anosognosia at the behavioural level (e.g., hemiplegic patients that try to walk) even if at the verbal level they recognize that they have a motor deficit (Jehkonen, Laihosalo, & Kettunen, 2006). Underlying mechanisms explaining anosognosia remain unclear (e.g., confusion, general intellectual loss, specific cognitive impairment) (Jehkonen et al., 2006; Vuilleumier, 2004). The presence of anosognosia in hemineglect has important drawbacks for recovery and the patient's engagement in therapy. For this reason, it is important in clinical practice to assess anosognosia (e.g., the Catherine Bergego scale, described in Section 1.1.4.1) and if possible, to prioritize rehabilitation of this disorder (though few rehabilitation strategies exist) before beginning the rehabilitation of hemineglect (Prigatano, 2009; Vuilleumier & Vocat, 2011).

Visual field deficits are mainly caused by lesions to the optic tract, the geniculostriate pathway or the striate cortex (Halligan, Marshall, & Wade, 1990). Damage at different stages of the visual pathway lead to loss of vision in different sectors of the visual field (e.g., hemianopia, quadranopia) (Bartolomeo, 2014). Visual field deficits can be measured by the Goldmann perimetry test. This measure consists in fixating (one eye covered) a central point and to detect lights differing in size and intensity presented in the patient's visual periphery (Talib, Dagnelie, & Boon, 2018). Association between visual field defects and hemineglect is well known (Sterzi et al., 1993), although double dissociations have also been reported (Halligan et al., 1990). It has been demonstrated that visual field deficits do not exacerbate hemineglect condition (Halligan et al., 1990). Visual field deficits can consciously be compensated by head and eye movements leading to scanning behaviour. On the contrary, patients with hemineglect exhibit difficulties in consciously scanning the visual scene and in taking into account the contralateral hemifield (Ting et al., 2011).

Motor impairments affect eighty percent of stroke patients (Langhorne, Coupar, & Pollock, 2009; Pulman & Buckley, 2013). Damage to the motor areas can result in a loss of motor control (i.e., voluntary production of movement), proprioception (i.e., awareness of limb position), spasticity (i.e., disordered muscle contraction), muscle shortening (i.e., contracture) and paresis (i.e., weakening of muscles) (Pollock et al., 2013).

Particular lesions of the primary motor cortex or pyramidal tract at the subcortical, capsular, medullar or spinal cord level lead to hemiplegia or hemiparesis on the contralesional side of the body (Classen et al., 1997; Fries, Danek, Scheidtmann, & Hamburger, 1993; Verstichel, 2014). Hemiparesis is a partial paralysis with decreased muscle strength or weakness in the contralesional limbs. Hemiplegia is a complete loss of contralesional motor function (Bourbonnais & Vanden Noven, 1989; Pulman & Buckley, 2013; Verstichel, 2014). According to Smidt and Rogers (1982), muscle strength is "the capacity of a muscle to produce the tension necessary for maintaining posture, initiating movement, or controlling movement during conditions of loading of the musculoskeletal system" (p.1283). Muscle weakness refers therefore to the inability to produce movement with a normal level of muscle force (Bourbonnais & Vanden Noven, 1989). Typically, in the upper limbs, the extensor muscles are more affected than the flexors, while it is the contrary in lower limbs (Larner, 2016). In the context of this thesis, focus will be made to hemiparesis of the upper limb.

The presence of motor difficulties has an immense impact on personal and domestic everyday life activities. The ability to perform tasks independently such as eating, cooking and dressing may cause destructive consequences on patients' mental health and well-being (Pulman & Buckley, 2013). Deficits can persist several months to years after the stroke incident in more than half of stroke patients (Pollock et al., 2013). Many authors recommend to use the International Model for Classification of Functioning, Disability and Health (ICF) for the assessment of motor impairments (World Health Organization, 2001). This classification is structured into three main components: body function and structures (e.g., range of motion, grip strength), activities (e.g., ability to dress) and participation (e.g., eating at a restaurant with friends). Motor learning principles typically guide upper limb rehabilitation with intensive practice, movement feedback, task-specific training, encouraging environments and movement assistance (Kitago & Krakauer, 2013). A recent review reported that the most beneficial interventions for upper limb rehabilitation were constraint-induce movement therapy, mental practice, mirror therapy, repetitive task practice and virtual reality (Pollock et al., 2013). Additionally, an increasing interest has been raised for the use of robot-assisted intensive therapy, configurable to the amount of assistance needed by the patient and using adapted feedback (Heins et al., 2017; Zhang, Li-Tsang, & Au, 2017). A recent review showed the beneficial transfer of robot-assisted therapy for daily life activities, arm function and arm muscle strength (Mehrholz, Pohl, Platz, Kugler, & Elsner, 2015).

While the impairment of the contralesional upper limb after a unilateral stroke has been largely evaluated and rehabilitated, evidence for disorders in the ipsilesional upper limb is rare as the limb has typically been considered as unaffected. However, there is some evidence that ipsilesional limb impairments can occur (Bustrén, Sunnerhagen, & Alt Murphy, 2017). Researchers have examined the kinematics of ipsilesional upper limb of hemiparetic stroke patients compared to healthy control participants while performing elbow movements of different amplitudes on a horizontal surface. Their set-up showed that brain-damaged patients had ipsilesional upper limb impairments in acceleration amplitude and in final position accuracy relative to the controls (Schaefer, Haaland, & Sainburg, 2007). The group of Cunha, de Freitas, and de Freitas (2017) compared ipsilesional hand function of hemiparetic stroke patients to age-matched healthy control participants on dexterity tasks such as the Jebsen and Taylor test, and on strength tests using a dynamometer. Their results indicated that while strength was preserved, dexterity of the ipsilesional hand was impaired. Bustrén et al. (2017) tested the functions of the ipsilesional upper limb of hemiparetic stroke patients in an activity of daily living, such as drinking from a glass (i.e., reaching and grasping the glass, transport it to the mouth, drinking, putting it back on the table, placing the hand in the initial position). In comparison to healthy control participants, ipsilesional arm movements were slower, less smooth, with a longer time in deceleration and an increased arm abduction while drinking.

Since hemiparesis and hemiplegia frequently co-occur with hemineglect, in particular after right hemispheric damage (Kerkhoff, 2001; Ogourtsova, Archambault, et al., 2015; Sterzi et al., 1993), it could be that they have a mutual influence on each other. Although no literature has clearly investigated the role of hemiparesis in patients with hemineglect and conversely, some studies got close to this question. For example, a recent study using robot-assisted training of repetitive and passive contralesional finger and wrist movements demonstrated an improvement of hemineglect on standardised tests (e.g., line cancellation test) (Varalta et al., 2014). Similarly, robot-assisted exercises of contralesional wrist, elbow and shoulder showed improved efficiency to reorient attention towards the contralesional hemifield compared to a control group receiving conventional treatment (i.e., visual scanning, see Section 1.1.6.1) (Choi et al., 2016). These results showed that manipulation of the contralesional limb improved hemineglect, supporting a link between the hemiparesis and hemineglect. It has also been demonstrated that in addition to physical rehabilitation, treatment of hemineglect significantly improved performance of hemiplegic patients in functional adaptation (e.g., Barthel Index, Rivermead Mobility Index) (Paolucci et al., 1996). These areas of research support the idea that motor impairments and hemineglect are closely overlapping and influence one another.

To summarize, hemineglect can co-occur with other deficits. Motor impairments have an essential role in this thesis since they affect the large majority of stroke patients having hemineglect. Although no clear evidence has been reported, hemineglect and hemiparesis seem to influence one another. Rehabilitation improving hemineglect has been shown to enhance hemiparesis and vice-versa. In the next section, the most effective conventional rehabilitation techniques of hemineglect will be reported.

1.1.6 Rehabilitation

One third of patients show persistent symptoms of hemineglect more than one year after the neurologic incident (Kerkhoff & Schenk, 2012). Many different treatments have been developed to try to reduce hemineglect symptoms and to make the patients as autonomous as possible (e.g., vestibular and optokinetic stimulation, mental imagery) (Luaute, Halligan, Rode, Rossetti, & Boisson, 2006). However, no specific rehabilitation guidelines have been established (Ting et al., 2011) and the heterogeneity of the hemineglect condition can make the choice of rehabilitation strategy challenging (Buxbaum et al., 2004). Most conventional therapies focus on egocentric hemineglect, probably because it is the type that is most widely investigated and that presents important disrupting symptoms in daily life. In this section, the most effective conventional therapies for egocentric hemineglect will be reviewed. Then, the few attempts to treat motor and allocentric hemineglect will be described.

1.1.6.1 Egocentric hemineglect

Several reviews have indicated that promising egocentric hemineglect rehabilitation comprise visual scanning, prisms adaptation and virtual reality (Luaute et al., 2006; Ting et al., 2011).

Visual scanning therapy (Diller, 1977) is one of the first and most studied hemineglect therapies, probably because it is easy to administer, has a low cost and provides positive results (Ting et al., 2011). The technique relies on the principle that hemineglect is a deficit of visual space exploration. The therapy consists in re-orienting voluntary visual scanning towards contralesional hemispace through practice, instructions and feedback from the therapist (Luaute et al., 2006). Different principles guide the rehabilitation strategy (Azouvi, Samuel, & Louis-Dreyfus, 2000b). First, the therapist begins the program with easy exercises and increases the difficulty level once the patient succeeds the exercise. For example, initially targets are presented alone on the ipsilesional side, and as the rehabilitation continues, targets are progressively moved to the contralesional side and dispersed among distractors (Antonucci et al., 1995), thereby increasing attentional load and exercise difficulty. Secondly, the patient receives feedback on their performance. Thirdly, the therapist plays an active role at the beginning of the treatment, verbally guiding and stimulating the exploration towards the contralesional hemifield, but progressively lets the patient build an internalised and automatic strategy. Finally, visual cues that serve as "anchor points" (e.g., a red line, a digit or a letter) are placed in the contralesional hemispace and used by the patient to first detect and then execute a task (Bowen & Wenman, 2002; Heilman et al., 2000; Kerkhoff, 2001; Lin, Cermak, Kinsbourne, & Trombly, 1996; Luaute et al., 2006).

The prism adaptation technique consists in wearing prismatic googles that shift vision to the left or right (e.g., by 10°) and asking the patient to make pointing movements to a target (Rossetti et al., 1998). Hemineglect patients with right lesions are exposed to an optical deviation to the right. Therefore, when pointing to the location of the perceived target, the hand will typically go to the right of the actual object. Using visual feedback and correction, patients will then compensate for the error, and make a movement toward the left. Across trials, patients learn to adapt their actions to the right-shift vision, leading to accurate pointing (Kerkhoff & Schenk, 2012). After training, hemineglect patients show a reduced contralesional bias on paper and pencil tests (e.g., figure copying, line bisection, reading test) that persists after two hours delay (Rossetti et al., 1998). Subsequent studies have confirmed and enlarged the beneficial effects of the prism adaptation technique, showing long-lasting behavioural benefits (Frassinetti, Angeli, Meneghello, Avanzi, & Làdavas, 2002; Serino, Barbiani, Rinaldesi, & Ladavas, 2009). The prism adaptation effect has also been generalized to hemineglect related cognitions such as wheel-chair driving (Jacquin-Courtois, Rode, Pisella, Boisson, & Rossetti, 2008), haptic spatial judgment (McIntosh, Rossetti, & Milner, 2002), representational neglect (Rode, Rossetti, & Boisson, 2001) and attention shifting between objects (Schindler et al., 2009).

Innovative therapies using virtual reality, serious games and robots have recently been developed for the rehabilitation of egocentric hemineglect (Choi et al., 2016; Y. M. Kim, Chun, Yun, Song, & Young, 2011; Mainetti, Sedda, Ronchetti, Bottini, & Borghese, 2013). Their main aim was to provide a motivating and secure environment to rehabilitate patients in tasks close to their daily life (Ting et al., 2011; Tomé, Pereira, & Oliveira, 2014b). One of the major advancement that these therapies provide is that they allow a constant evaluation of patients' performance and can adapt the difficulty level of rehabilitation to the level of the patient. Therefore, they challenge the patient at the boundary of their capacities until maximum recovery is achieved (Gouaïch, Hocine, Van Dokkum, & Mottet, 2012). More details about these rehabilitation techniques will be given in the Chapter 6 of this thesis.

Spatial cueing has also demonstrated positive results in attention reorientation and is of particular interest in this thesis. In patients with hemineglect, Butter, Kirsch, and Reeves (1990) showed that dynamic visual cues compared to static cues (i.e., squares in motion or not) presented on the contralesional side of a task, significantly improved performance on the line bisection test. Auditory cues, either verbal or non-verbal, have also shown encouraging results in reorienting attention towards the contralesional hemispace (Fanthome, Lincoln, Drummond, & Walker, 1995; Hommel et al., 1990). The use of the contralesional limb as a spatial motor cue (also named limb activation therapy) has been tested in hemineglect patients and associated with visual scanning treatment (Brunila, Lincoln, Lindell, Tenovuo, & Hämäläinen, 2002). Different manners of mobilizing the contralesional limb can lead to increased attraction to contralesional space. Robertson, North, and Geggie (1992) demonstrated that using the contralesional arm (even if hemiparetic) as a perceptual anchor in the contralesional hemifield improved visuo-spatial exploration and showed less hemineglect on a variety of paper and pencil tests. Also, tapping as many times as possible on the contralesional side has been shown to improve results on paper and pencil tests and everyday task performance (Wilson, Manly, Coyle, & Robertson, 2000). One may think that the spatial motor cues were only possible for patients having minimal motor function. However, research shows that passive moments of the contralesional arm (e.g., arm abduction and adduction, finger, wrist, elbow movements) made by mechanical devices or a robot, simultaneous to ipsilesional arm activation (Frassinetti, Rossi, & Ladavas, 2001) or alone (Choi et al., 2016; Varalta et al., 2014) demonstrated improvements of hemineglect symptoms.

1.1.6.2 Allocentric hemineglect

Contrary to egocentric hemineglect, very few studies concerning allocentric hemineglect rehabilitation have been reported in the literature. A recent paper demonstrated that although prism adaptation training (see Section 1.1.6.1) improves egocentric hemineglect, no positive effect of prism adaptation have been reported for allocentric hemineglect (e.g., Apples cancellation test, line bisection test) (Gossmann, Kastrup, Kerkhoff, López-Herrero, & Hildebrandt, 2013). However, a study run on single cases showed that visual scanning therapy (see Section 1.1.6.1), where picture and figure recognition was emphasized (i.e., noticing divergences between complete and incomplete figures), caused significantly enhanced improvements in allocentric hemineglect (Pachalska, Franczuk, MacQueen, & Talar, 2004). In another paper, Medina et al. (2013) investigated if transcranial Direct Current Stimulation (tDCS) could influence visuo-spatial processing of egocentric and allocentric frames of reference in healthy participants. The participants were required to perform a computerised target detection task where the target was a circle with a gap (either on the left or on the right) presented either on the left or on the right side of the monitor. This task was performed before, during and after tDCS stimulation. Results indicated that tDCS stimulation (right anodal / left cathodal) relative to sham, facilitated allocentric visuo-spatial processing, indicating potential promising results for a future treatment of allocentric hemineglect.

1.1.6.3 Motor hemineglect

Since the pure form of motor hemineglect is rare and not well understood or evaluated, the development of adapted therapies have received very little attention in the literature (Saevarsson, 2013; Sampanis & Riddoch, 2013). The few suggestions for spatial motor hemineglect rehabilitation have shown conflicting results (e.g., Saevarsson & Kristjánsson, 2013; Striemer & Danckert, 2010) and will therefore not be described here. However, the few proposals of rehabilitation techniques for personal motor hemineglect will be reported.

Authors have suggested that personal motor hemineglect can be reduced after cold water caloric vestibular stimulation (Rode et al., 1998). This technique is frequently used for the treatment of visuo-spatial hemineglect and consists of irrigating the external ear canal with cold water for thirty seconds. The authors tested two groups of hemiplegic patients, one with visuo-spatial and personal motor hemineglect, and the other with only hemiplegia. After vestibular caloric stimulation, they found a reduction of the motor deficit only in the group with hemineglect. The authors believed that this reduction was only found in the group with hemineglect because of the presence of personal motor hemineglect, which benefited from the treatment. In other words, the beneficial effect of vestibular stimulation on the motor deficit could be explained by an improvement of the personal motor hemineglect component. More evidence is needed to verify these results, but if correct, it suggests that vestibular stimulation could be a potential rehabilitation strategy for personal motor hemineglect. However, it should be noted that vestibular stimulation only demonstrated short-term effects on visuo-spatial hemineglect, which could be an obstacle for the rehabilitation of personal motor hemineglect. Other authors suggested the use of new techniques for personal motor hemineglect rehabilitation such as Transcranial Magnetic Stimulation (TMS) or transcranial Direct Current Stimulation (tDCS) to increase the activity of the damaged hemisphere or decrease the over-activity of the non-damaged hemisphere (Sampanis & Riddoch, 2013). Indeed, in line with the theory of Kinsbourne (1993), these techniques have shown positive effects on visuo-spatial hemineglect by decreasing the over-activity in the contralesional hemisphere and in turn improving contralesional performance (Koch et al., 2008). Additionally, improvements of visuo-spatial hemineglect have also been demonstrated when using these stimulation approaches in combination to another treatment, for example prism adaptation technique (Làdavas et al., 2015; O'Shea et al., 2017). Therefore, these brain stimulation methods could provide a potential promising tool for personal motor hemineglect rehabilitation (Sampanis & Riddoch, 2013).

To summarize this rehabilitation section, given the heterogeneity of the hemineglect condition, the choice of treatment must match known deficits exhibited at hemineglect evaluation. Egocentric hemineglect has received a lot of attention leading to the development of several effective treatments. Nevertheless, none of the current techniques has been designated as gold standard. Concerning allocentric and motor hemineglect, therapies are still at a very experimental level, with no treatment routinely used in clinical practice. It is therefore unclear which kind of training is suitable for these forms of hemineglect. The next section will summarise the main objectives of this thesis.

1.2 Outline of the thesis

The objective of this introduction was to provide an overview of the literature and current understanding of hemineglect. The hemineglect condition, occurring frequently after a stroke incident, can affect different modalities and different frames of reference (Plummer et al., 2003). In the context of this thesis, three types of hemineglect were addressed: visuo-spatial egocentric and allocentric hemineglect, and motor hemineglect with a particular interest for the action kinematics impairments.

The evaluation of hemineglect is of crucial importance since it guides the choice of appropriate therapy and in turn patient recovery (Jehkonen et al., 2000). However, despite the necessity of administrating several assessments to obtain a comprehensive diagnosis, due to time pressure in clinical routine, therapists often have to make a selection between tests (Petzold et al., 2014). The majority of existing hemineglect assessments concern visuo-spatial egocentric hemineglect, for which both conventional and innovative tests have been developed. As a consequence, this type of hemineglect is probably the most evaluated in clinical practice. Several allocentric tests exist, but only a few are objective and quantified. Concerning motor hemineglect, despite the various experimental paradigms tested, there is no validated evaluation, which significantly limits the consideration of this hemineglect form in clinical routine. In daily practice, the evaluation of hemineglect patients therefore mainly concerns perception and not action.

Existing therapies are largely based on egocentric hemineglect, with no validated clinical rehabilitation for allocentric and motor hemineglect. Despite these existing treatments, one third of patients demonstrate persistent symptoms of hemineglect more than one year after the neurologic incident (Kerkhoff & Schenk, 2012). Therefore, a need to continue the development in this area remains. The use of new technologies such as serious games and robots offer promising methods to train patients, while providing motivating and secure environments, as well as personalised auto-adapted rehabilitation (Gouaïch et al., 2012; Ting et al., 2011; Tomé et al., 2014b).

Besides the functional impairments caused by hemineglect, stroke patients are frequently affected by other deficits. One of the most important co-deficits is hemiparesis, which is a long-lasting motor impairment (Kerkhoff, 2001; Ogourtsova, Archambault, et al., 2015; Pollock et al., 2013). Despite the co-occurrence of the two conditions, to our knowledge, no literature has clearly investigated their mutual influence. Some studies got close to this question by showing that treatment of hemineglect can improve hemiparesis and vice versa (Brunila et al., 2002; Paolucci et al., 1996). However, further investigations are needed to better understand the links between hemineglect and hemiparesis.

The aim of the present thesis was therefore to make a step forward in the assessment, rehabilitation and understanding of hemineglect through innovations in perception and action measures. Firstly, we wanted to provide a comprehensive and sensitive assessment of visuo-spatial hemineglect and associated action kinematics. Secondly, we wanted to provide an innovative hemineglect rehabilitation using an auto-adapted serious game that combined perception and action. Finally, we wanted to enlarge the understanding of the hemineglect condition, investigating factors that modulate perception and action links in hemineglect.

In Chapter 2, the aim was to develop the first stage of an innovative robot test named the MonAmour. The test consisted of a target search task combining the evaluation of visuo-spatial egocentric and allocentric hemineglect. In this first stage, the goal was to validate the “pushing” version of the MonAmour against three standardised tests with stroke patients (with and without hemineglect), to measure reliability and to establish norms on healthy control participants. The “pushing” version of the MonAmour required participants to make either a push or pull response on the robot end-effector depending upon the target type (with the end-effector remaining fixed at the starting position).

In Chapter 3, the aim was to extend Chapter 2 and deepen the evaluation of egocentric hemineglect patients. We measured their reaching action kinematics towards contralesional versus ipsilesional hemispace, and compared them to the actions of healthy control participants. We used a “reaching” version of the MonAmour test, with two different attentional load conditions, and we measured responses made with both hands. The “reaching” version of the MonAmour required the participants to make a reaching response by moving the robot end-effector to a defined position depending upon the target type.

In Chapter 4, we investigated links between hemineglect and hemiparesis. The aim was to measure the influence of motor impairment on visuo-spatial perception using the pushing and reaching versions of the MonAmour test. We compared the performance of three groups: stroke patients with hemiparesis with or without hemineglect, and healthy control participants.

In Chapter 5, we presented the first stage of the development of a combined motor and cognitive serious game, named the ROB*i*GAME, focusing on hemiparesis and hemineglect rehabilitation. The aim was to run a feasibility study addressing the usability of a sandwich shop serious game with stroke patients and with therapists.

In Chapter 6, we further developed the ROB*i*GAME. The aim was to define two methods to objectively auto-adapt the difficulty of a serious game for hemineglect rehabilitation, in correspondence to the patient’s individual performance. This chapter investigated how to moderate game difficulty by manipulating attentional load and cue types.

In Chapter 7, we discussed the findings of the thesis with reference to the three principal objectives presented above and the current literature. We discussed the limitations of the research, and we provided potential future perspectives that could extend the findings presented in this thesis.

Chapter 2

Robot diagnosis test for egocentric and allocentric hemineglect

Chapter 2

Robot diagnosis test for egocentric and allocentric hemineglect

Abstract

Objective: Patients with hemineglect fail to respond to egocentric stimuli or allocentric parts of stimuli contralateral to the brain lesion. The clinical diagnosis of hemineglect mainly involves evaluation of the egocentric form, while less sensitive standardised tests exist for other forms. Our global aim is to develop an innovative integrative robot measure, the MonAmour test, combining the assessment of egocentric, allocentric and motor hemineglect. Here, we present the egocentric and allocentric evaluations. **Methods:** Thirty-five first stroke patients (25 hemineglect) and 56 age-matched healthy control participants were assessed on the index test (MonAmour) and on three reference standard tests (Bells test, Apples test and Neglect subtest of the Test for Attentional Performance). Based on controls' performance, normative data were created. Validity was evaluated between the MonAmour and the reference standard tests through correlations and test sensitivity/specificity. Reliability of the MonAmour was measured with test-retest and minimal detectable change. **Results:** Results demonstrated moderate to strong correlations between the MonAmour and the reference standard tests (r = .40 - .88, p < .001 – p= .016). The sensitivity was high (50% - 96%), with accurate diagnosis of patients with hemineglect, and reliability was excellent (Intraclass Correlation Coefficient = .79 - .95, p< .001). **Conclusions:** The MonAmour robot test is a valid, sensitive and reliable tool that can diagnose egocentric and allocentric hemineglect. Future studies will deepen the assessment and understanding of the different forms of hemineglect by testing the motor component of the test in order to use this accurate and integrative measure in daily clinical routine. **Registration:** ClinicalTrials.gov (NCT02543424).

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2.1 Introduction

Each year, 15 million people worldwide are affected by stroke, frequently leading to severe impairments in cognitive and/or motor function (Mackay et al., 2004). Cognitive disorders after stroke typically affect memory, language, orientation and attention (Jaillard, Naegele, Trabucco-Miguel, LeBas, & Hommel, 2009; Tatemichi et al., 1994). Among the attention impairments, hemineglect is described as a failure to report or respond to stimuli contralateral to a brain lesion, and occurs in approximately twenty-three percent of stroke cases (Appelros et al., 2002; Heilman, Watson, & Valenstein, 1993; Kamtchum Tatuene et al., 2016). Large stroke cohort research has demonstrated that hemineglect is more common following right than left brain damage (Ringman et al., 2004).

Hemineglect is a heterogeneous syndrome that affects different modalities, frames of reference and portions of the space (Rode & Pisella, 2011). Hemineglect can affect the sensory, motor or representational modalities. Sensory hemineglect is defined as an inability to perceive contralesional visual, auditory or tactile stimuli (Plummer et al., 2003), whereas motor hemineglect is described as an underuse of the contralesional limb in bimanual tasks (e.g., opening a bottle) despite normal strength, reflexes and sensitivity (Laplane & Degos, 1983; Sampanis & Riddoch, 2013; Siekierka-Kleiser et al., 2006). Motor hemineglect can also refer to a failure to execute a movement (e.g., showing delayed reaction time, slowness in the movement speed) towards the contralesional hemifield (using the ipsilesional limb) (Heilman et al., 1985; Mattingley et al., 1992). Representational hemineglect is the failure to report contralesional internally generated spatial scenes (Bisiach & Luzzatti, 1978; Kerkhoff, 2001). Hemineglect can also depend on reference frames. Patients that experience egocentric hemineglect fail to respond to contralesional stimuli from a body-centered viewpoint, whereas patients that manifest allocentric hemineglect fail to respond to the contralesional side of stimuli irrespective to their viewpoint (Rorden et al., 2012). Patients who fail to explore the contralesional part of their body when grooming or dressing are said to be affected by personal hemineglect. Spatial peripersonal hemineglect refers to a failure to respond to contralesional stimuli within reach. This form differs from spatial extrapersonal hemineglect (i.e., the space beyond arm's reach, explored through oculomotor movements; Plummer et al., 2003). Dissociations between the different forms of hemineglect have been reported in the literature, suggesting that the different forms may be independent deficits (Marsh & Hillis, 2008; Rorden et al., 2012).

Different models have been provided to explain hemineglect. These can be distinguished according to the nature of the hemineglect. For attentional hemineglect, Heilman and colleagues (1993) suggests a dominance of the right hemisphere that orients attention to both sides of space, whereas the left hemisphere orients attention primarily to the right side of space. After a left hemispheric lesion, attention can still be orientated to the right hemispace thanks to the right hemisphere.

However, a right hemispheric lesion causes reduced attention to the left hemispace, explaining the high prevalence of patients exhibiting left hemineglect. Kinsbourne (1993) hypothesizes a mutual inhibition of hemispheres, with a dominance of the left one. Lesions to the right hemisphere explain the prevalence of left hemineglect due to the hyper-attention towards the right hemispace. For representational hemineglect, Bisiach and Luzzatti (1978) suggest that the mental representation of space is disrupted by a lesion, causing an enlargement of space representation ipsilateral to the lesion. The model of Rizzolatti et al. (1997) combines attentional and representational models, claiming that action planning defines space representation, which will in turn influence attention. Lesions to premotor structures lead to hemineglect in different portions of space. Nowadays, these and other interpretative hypotheses remain debated in the literature, and no single model explains the complexity of hemineglect, perhaps supporting the assumption that hemineglect may not be a unitary condition (Ting et al., 2011).

The heterogeneity of the syndrome makes diagnosis challenging (Grattan & Woodbury, 2017). One-third of hemineglect patients still show symptoms one year after stroke, creating difficulties in daily life activities (Karnath, Rennig, Johannsen, & Rorden, 2010). Therefore, there is a need to better assess the different forms of hemineglect in order to better define the conditions, and to increase the patient’s quality of life using better targeted treatments. Hemineglect is typically assessed with several paper and pencil clinical measures. The most frequently used tests are the cancellation tests (e.g., letters, lines, stars and bells cancellation tests), principally because they are easy to administer and allow for a quantitative assessment of egocentric peripersonal hemineglect (Azouvi et al., 2000a; Bickerton et al., 2011; Bowen et al., 1999; Halligan, Cockburn, & Wilson, 1991). Line bisection tests (Schenkenberg et al., 1980) and figure copying tests such as the Clock, the Daisy or the Ogden scene drawings are also commonly integrated in the evaluation of hemineglect (Bailey et al., 2000; Ogden, 1985). The Apples cancellation, line bisection and figure copying tests allow simultaneous assessment of egocentric and allocentric peripersonal hemineglect. However, the figure copying tests require some subjective interpretation for evaluation, whereas cancellation and line bisection tests are accurate and require no subjectivity (Azouvi, Samuel, et al., 2002; Bailey et al., 2000).

Several researchers have suggested that paper and pencil tasks used for the diagnosis of hemineglect are not sensitive enough to show slight impairments (Bonato, 2012; Bonato & Cutini, 2016; Buxbaum et al., 2012). The development of computerised tests adds crucial value to paper and pencil tests, enhancing sensitivity through stimuli randomization and more precise measures (Erez et al., 2009; Zimmermann & Fimm, 2002). These developments increasingly involve new technologies such as Virtual Reality (VR). Fordell et al. (2011) developed VR-DiSTRO which transposes four paper and pencil tests in a virtual environment (lines bisection, stars cancellation, baking tray test and a visual extinction test). Their aim was to record more information such as start point, end point and scanning patterns. Similarly, another study demonstrated on two hemineglect single cases the usability of a head-mounted display for line cancellation tests (Tanaka et al., 2010). Ecological tests have also been developed. In Kim and colleagues (2010), patients cross a street and their head's deviation angle and reaction time are measured. In Buxbaum and colleagues (2012), patients walk along a track and report animal statues and the colour of trees, while avoiding collisions with dynamic distractor objects (i.e., Virtual Reality Lateralized Attention Test; VRLAT).

Unlike perceptual forms of hemineglect, diagnosis of motor hemineglect is rare. Although several experimental studies have presented tasks that assess different motor forms (Bartolomeo et al., 1998; Chiba, Yamaguchi, & Eto, 2005), to our knowledge, these tasks are not yet used and standardised for routine clinical practice. Nevertheless, current developments in robotic devices provide new opportunities to measure action in the clinic. In the last years, the use of robots has raised an increasing interest in post-stroke neurological rehabilitation, especially in upper limb rehabilitation of hemiparesis and hemiplegia (Gilliaux et al., 2014; Mehrholz et al., 2015), but also in hemineglect rehabilitation (Choi et al., 2016; Heins et al., 2017; Varalta et al., 2014). For example, robot-assisted exercises of the wrist, elbow and shoulder while playing a game demonstrated a reorientation of attention towards the contralesional hemifield (Choi et al., 2016). In this context, the robot is defined as a programmable mechanical tool that allows the movement of a patient's limb across a given range of motion (Bien & Stefanov, 2004). The robot interacts with the patient's actions, either in a 'passive mode' where the user is passive and the robot completes the upper limb movement, in an 'active mode' where the user is active and the robot does not provide any assistance (but measures performance), and in an 'active-passive mode' where the robot moderates the provided assistance based on the user's needs. The use of a robot, in the active mode, for diagnosis of motor hemineglect could provide an accurate measure of motor responses. As far as we know, no study has investigated the use of robot interaction to diagnose motor hemineglect in clinical practice to this day.

Previous research has shown that the assessment of hemineglect through several tests gives a more sensitive diagnosis than any unique measure (Azouvi, Samuel, et al., 2002). Despite these recommendations, clinicians do not have the time to administer an entire quantitative battery and often make choices for the most appropriate tests (Petzold et al., 2014). Additionally, therapists spend time scoring the tests (Fordell et al., 2011). These demands can lead to a loss of diagnosis information to adequately guide the rehabilitation (Grattan & Woodbury, 2017).

Our global objective in this project was to develop and validate a unique clinical test for the combined quantitative evaluation of egocentric, allocentric and motor hemineglect using a robot. As in computerised and new technologies tests, the robot provides multiple sensitive measures (e.g., reaction time, movement kinematics), a reduced learning effect through the randomization of stimuli presentation, and a standard administration of the tests between therapists. Combined, these elements allow the therapist to save time by providing a sensitive simultaneous assessment of three forms of hemineglect, and an immediate scoring that is compared to norms.

In order to achieve this global objective, the present paper focused on the egocentric and allocentric parts of the test; the MonAmour. Firstly, we created norms for the MonAmour from healthy control participants. Secondly, we validated the test on stroke patients (with and without hemineglect) using correlations and sensitivity/specificity analyses against three reference standard tests, namely the Bells test (Gauthier et al., 1989), the Apples test (Bickerton et al., 2011) and the Neglect subtest from the Test for Attentional Performance (TAP) (Zimmermann & Fimm, 2002). Finally, we analysed the reliability of the MonAmour through the test-retest measure and Minimal Detectable Change (MDC). Future studies will integrate and investigate the motor component of the MonAmour test.

2.2 Methods

2.2.1 Participants

Brain-damaged patients were recruited using a consecutive sampling from the neuropsychological and physical medicine and rehabilitation departments of the Cliniques universitaires Saint-Luc and the Centre Hospitalier Neurologique William Lennox in Belgium from April 2015 to December 2017. Patients were selected according to the following criteria: (1) presence of an ischemic or hemorrhagic first stroke; (2) presence of hemineglect and/or hemiparesis clinical diagnosis documented through neurological evaluation reports and; (3) a good understanding of the task instructions. We recruited patients without a hemineglect diagnosis (inclusion criteria n°2) in order to test whether our new measure detected patients with and without hemineglect. Exclusion criteria were the presence of other neurological conditions such as dementia or orthopedic illness that limits the function of the upper limb. We recruited patients without a hemineglect diagnosis (inclusion criteria n°2) in order to test whether our new measure detected patients with and without hemineglect.

In addition to the patients' group, neurologically healthy adult participants paired by mean patient age were recruited. Presence of any orthopaedic illness limiting the upper limb's function was an exclusion criterion. The Saint-Luc Biomedical Hospital-Faculty Ethics Committee approved the research protocol prior to any experimentation and all participants volunteered to participate to the study providing a written informed consent. The study was registered at ClinicalTrials.gov (NCT02543424).

2.2.2 Materials

2.2.2.1 Apparatus

The REAplan® robot (Axinesis; Figure 1) was used for the development of the MonAmour hemineglect test. The REAplan ® is a planar end-effector robot with position and force sensors allowing for precise action measures in the horizontal plane. This horizontal plane had dimensions of 93 x 52 cm. The robot has a visual interface for the patient (1920 x 1080 pixels), and a separate monitor for the therapist. The robot has already been used for the assessment and treatment of upper limb motor impairments carrying it on the horizontal plane (Gilliaux et al., 2014). In the context of the present study, the end-effector of the robot remained in a fixed position, with only the force sensors triggered to record reaction times when pushing or pulling the end-effector.

Figure 1. The REAplan® end-effector robot (permission to use image allowed from Axinesis; Copyright), with: (a) a handle for interaction that measures position and force, (b) a visual interface for the participant, and (c) a visual interface for the experimenter / clinician.

2.2.2.2 Index test

The MonAmour test (Figure 2; created by Montedoro., V and Alsamour., M) consisted of a target search task requiring participants to find a gray colored musical conductor (the target) randomly presented among black colored musical instruments of four different types (the distractors). The different colors of the target and distractors (70 x 70 pixels) were defined after a pilot study to optimize the difficulty of the task (all stimuli in the same color made the test too difficult even for control participants, therefore the grayness was moderated to make the test possible but still challenging). The targets could be complete (full musical conductor) or incomplete (musical conductor missing part of the left or right arm) measuring egocentric and allocentric forms of hemineglect. When participants perceived a complete target, they were instructed to make a push response using the end-effector of the REAplan® robot towards the conductor's baton, and when the target was incomplete, they were instructed to make a pull response, towards the conductor's musical stand. Catch trials, where no target was presented, were included in order to verify that the participants understood correctly the instructions and to measure impulsive responses. For the catch trials, participants were instructed to make no response on the end-effector.

As in the three standardised tests administered in the present study (see description below), we used a high attentional load display in order to detect hemineglect (Azouvi, Samuel, et al., 2002; Gauthier et al., 1989; Kaplan et al., 1991). For each trial, a single target and 119 distractors were organized using an invisible grid composed of five columns and six rows (30 cells), with a balance of stimuli across the left, right, upper and lower spaces (in accordance to standardised tests such as the Bells and Apples tests). The target was always presented in the center of one grid cell, with three randomly presented distractor stimuli. In the remaining 29 cells, four distractor stimuli were randomly placed. The test was composed of 100 trials, with 30 complete target trials, 30 incomplete left target trials, 30 trials incomplete right target trials and 10 catch trials (defined in accordance to the proportion of target-distractors in the Apples test). Participants had a maximum of 7000 ms to make a response. If the participants made no response, the trial ended and the next trial initiated. Each trial was separated by a central musical note acting as a fixation cross (presented for 1500 ms) in order to standardise the starting point of the space exploration across participants. Breaks were possible at any time during the test. Before beginning the MonAmour test, standardised instructions and ten practice trials were given to the participants. During the practice trials, the different types of target and catch trials were presented to the participants in the same proportion as in the main test, but the targets were placed near the centre of the screen facilitating detection and allowing patients with hemineglect to understand the test correctly.

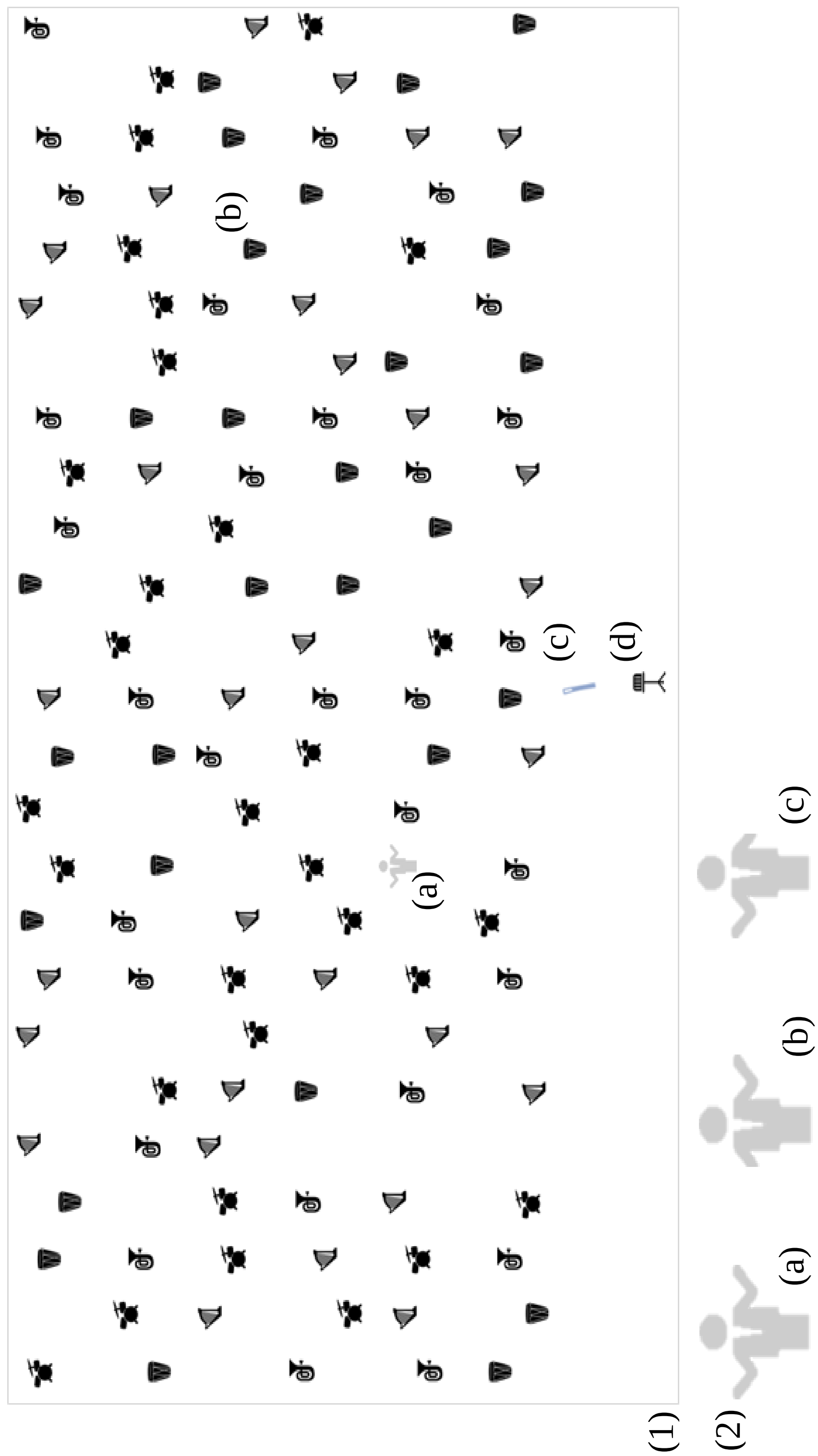


Figure 2. The MonAmour test, with: (1) the target search task with (a) the target musical conductor, (b) the four different types of distractor instruments, (c) the conductor's baton, (d) the conductor's musical stand; and (2) the three types of target (a) complete target, (b) left incomplete target, and (c) right incomplete target.

The MonAmour test provided the possibility to assess overall performance through the percentage of total omissions (i.e., where the participant failed to respond within 7000 ms to targets, independent of their position in the space) and total mean reaction time (i.e., mean reaction time of correct responses, independent of target position in the space). To define egocentric hemineglect in the MonAmour test, two variables were calculated. Firstly, the percentage of omissions asymmetry corresponded to the difference between contralesional percentage of omissions (i.e., where the participant failed to respond within the time limit to targets presented in the two contralesional columns) and ipsilesional percentage of omissions (i.e., where the participant failed to respond within the time limit to targets presented in the two ipsilesional columns). Secondly, mean reaction time asymmetry referred to the difference between contralesional and ipsilesional mean reaction time for correct responses. For these two first measures, positive values indicated reduced performance in the contralesional compared to ipsilesional space, whereas negative values indicated reduced performance in the ipsilesional compared to contralesional space. Allocentric hemineglect was evaluated through false positive responses, where an incomplete target is responded to as if it was a complete target (i.e., where the participant made a push response to the musical conductor missing part of the contralesional or ipsilesional arm). To establish the presence of allocentric hemineglect, the percentage of false positive responses asymmetry was calculated (i.e., the difference between false positive responses on contralesional incomplete targets vs. ipsilesional incomplete targets). Positive values indicated that allocentric contralesional parts of stimuli were responded to as full targets, while negative values indicated allocentric ipsilesional parts of stimuli were responded to as full targets.

2.2.2.3 Reference standard tests

Three standardised hemineglect diagnosis tests were administered to the patients in order to validate the MonAmour test. The Bells test (Gauthier et al., 1989) was chosen because it has proven over the years to be highly sensitive to detect hemineglect (Basagni et al., 2017; Oliveira de CR et al., 2016; Vanier et al., 1990). The Apples test was chosen due to its ability to diagnose allocentric hemineglect (Basagni et al., 2017; Bickerton et al., 2011). We included the computerised Neglect subtest of the TAP as it allows assessment of hemineglect through both omissions and mean reaction time measures (matching the MonAmour test) (Zimmermann & Fimm, 2002).

The Bells cancellation test is an egocentric visual hemineglect test that requires patients to circle 35 bell target stimuli amongst 280 distractor stimuli evenly distributed on a sheet of paper (within an invisible grid of seven columns) placed in front of the patient. The percentage of total omissions (independently of the space) and the percentage of omissions asymmetry between contralesional and ipsilesional hemispace (i.e., difference of omissions between the three contralesional and three ipsilesional columns depending on the patient's lesion side) were calculated.

The Apples cancellation measures both egocentric and allocentric hemineglect. Patients were asked to cross out complete apples (50) and ignore incomplete apples (50 having a right opening and 50 having a left opening). Full and incomplete apples were equally distributed across an invisible grid of five columns and two rows. The recorded variables were the percentage of total omissions (independently of the space), the percentage of omissions asymmetry between contralesional and ipsilesional hemispace (i.e., difference of omissions between the two contralesional and two ipsilesional columns depending on the patient's lesion side) and the percentage of false positives asymmetry (i.e., the difference between response selected apples with a contralesional and ipsilesional opening).

The Neglect subtest is a computerised task where patients detect a blinking increasing number (target) as soon as possible among static numbers (distractors). Over the full task, 44 single targets are presented equally and randomly across an invisible 4 square grid (2 columns and 2 rows), with the targets appearing at variable time intervals. To control for hemianopia, patients could move their eyes during the task. The percentage of total omissions, the total mean reaction time for correct responses, the percentage of omissions asymmetry between the contralesional and ipsilesional hemifield, and the mean reaction time asymmetry for correct responses were analysed.

2.2.3 Procedure

For the patients, the testing was divided into two sessions (30-45 minutes) separated by an interval of 2-5 days. During the first session, participants performed the MonAmour test and the three standardised tests. The aim of this first session was to validate the MonAmour test against the standardised tests and, establish sensitivity and specificity. The second session involved doing the MonAmour test a second time in order to measure reliability and calculate the minimal detectable change. The ipsilesional hand was used for all the tests. For the healthy control participants, the testing consisted of a single session (30 min) where they were asked to do the MonAmour tests once with their dominant hand in order to create norms.

For the MonAmour test, participants were sat comfortably in a chair without wheels, centered in front of the participant's monitor of the REAplan ® robot. Participants were sat at the edge of the robot's horizontal plane, approximately 52 cm from the monitor. The handle of the robot was centered at the edge of the horizontal plane. The height of the horizontal plane of the robot was adjusted to correspond to the navel position of the participant (using an automatized height-adjusted table). The feet of the participants touched the ground. For security reasons, patients on wheelchair were not moved from their chair. For the standardised tests, participants remained at the same location, and the end-effector of the robot was removed so that the horizontal plane of the robot became a table. The tests were either administrated in a laboratory at the Faculty of psychology at the Université catholique de Louvain or in one of the two hospitals were the patients were recruited.

2.2.4 Data analyses

Statistical analyses were performed using SPSS software (IBM, SPSS statistics 25). The main objectives of the analyses were to provide norms, criterion validity and reliability.

Norms (95% confidence intervals) for the MonAmour test were created from the performance of the healthy control participants to detect patient's impairments (> $\bar{X}$+ 1.96*standard deviation; *SD*). For overall performance diagnosis, patients had to show a deficit either on percentage of total omissions or on total mean reaction time. To be diagnosed as having egocentric hemineglect, patients had to be impaired either on percentage of omissions asymmetry or on mean reaction time asymmetry. To be diagnosed with allocentric hemineglect, patients had to be impaired on false positive asymmetry.

Criterion validity consisted in verifying if the results of the MonAmour test were associated to the results of the standardised tests (Mokkink et al., 2012). This was investigated in the patient group using correlation coefficient analyses between the MonAmour test and each of the standardised tests. Following Cohen (1988), correlations can be rated as weak ($0.1 \leq r < 0.3$), moderate ($0.3 \leq r < 0.5$) or strong ($r \geq 0.5$). The validity of the MonAmour was also assessed calculating sensitivity (ability of the test to detect people with hemineglect; $\frac{True\ positive}{True\ positive + False\ negative}$) and specificity (ability of the test to detect people without hemineglect; $\frac{True\ negative}{False\ positive + True\ negative}$) using respective norms of the tests (Greenhalgh, 1997). Regarding overall performance, patients were classified according to whether they showed an impairment on the MonAmour test and on at least one of the three standardised tests (comparison to their respective norms for the percentage of total omissions and the total mean reaction time). Regarding egocentric hemineglect, patients were characterized according to whether they showed hemineglect on the medical clinical diagnosis and on the MonAmour test (comparison to our norms for percentage of omissions asymmetry and mean reaction time asymmetry). For egocentric hemineglect, patients were also categorized according to whether they were impaired on the MonAmour and on at least one of the three standardised tests of hemineglect (comparison to their respective norms for percentage of omissions asymmetry and mean reaction time asymmetry). Concerning allocentric hemineglect, patients were diagnosed according to whether they presented allocentric hemineglect on the MonAmour and on the Apples test (comparison to their respective norms for the percentage of false positives asymmetry).

Reliability analyses were run on a subgroup of 23 patients who were available to perform the task twice. An Intraclass Correlation Coefficient (ICC) between the two repeated measures of the MonAmour from the same person were performed (Koo & Li, 2016; Shrout & Fleiss, 1979). The ICC based on mean rating and absolute agreement parameters were calculated using a two-way mixed model. Reliability was rated as poor (ICC ≤ 0.40), moderate (0.40 < ICC < 0.75), or excellent (ICC ≥ 0.75) (Andresen, 2000). For future use of the MonAmour in the context of assessing patients' performance improvement (e.g., pre- and post-treatment measures or spontaneous recovery), the MDC was calculated. The MDC refers to the minimal change needed over two repeated measures to show an actual significant improvement in the patient's performance that cannot be attributed to a measurement error. For example, if the MDC of the percentage of omissions asymmetry was 9%, the patient had to have at least a difference of 9.1% between the first and second MonAmour test administration to demonstrate an improvement of the patient's performance. The MDC was calculated using a two-sided 95% confidence level ($MDC_{95} = \text{Standard Error of Measurement } (SEM) * 1.96 * \sqrt{2}$; the SEM = $SD * \sqrt{1 - ICC}$ where SD corresponded to the standard deviation of all observations in the test-retest) (Chuang et al., 2015; Kovacs et al., 2008; Wagner, Rhodes, & Patten, 2008).

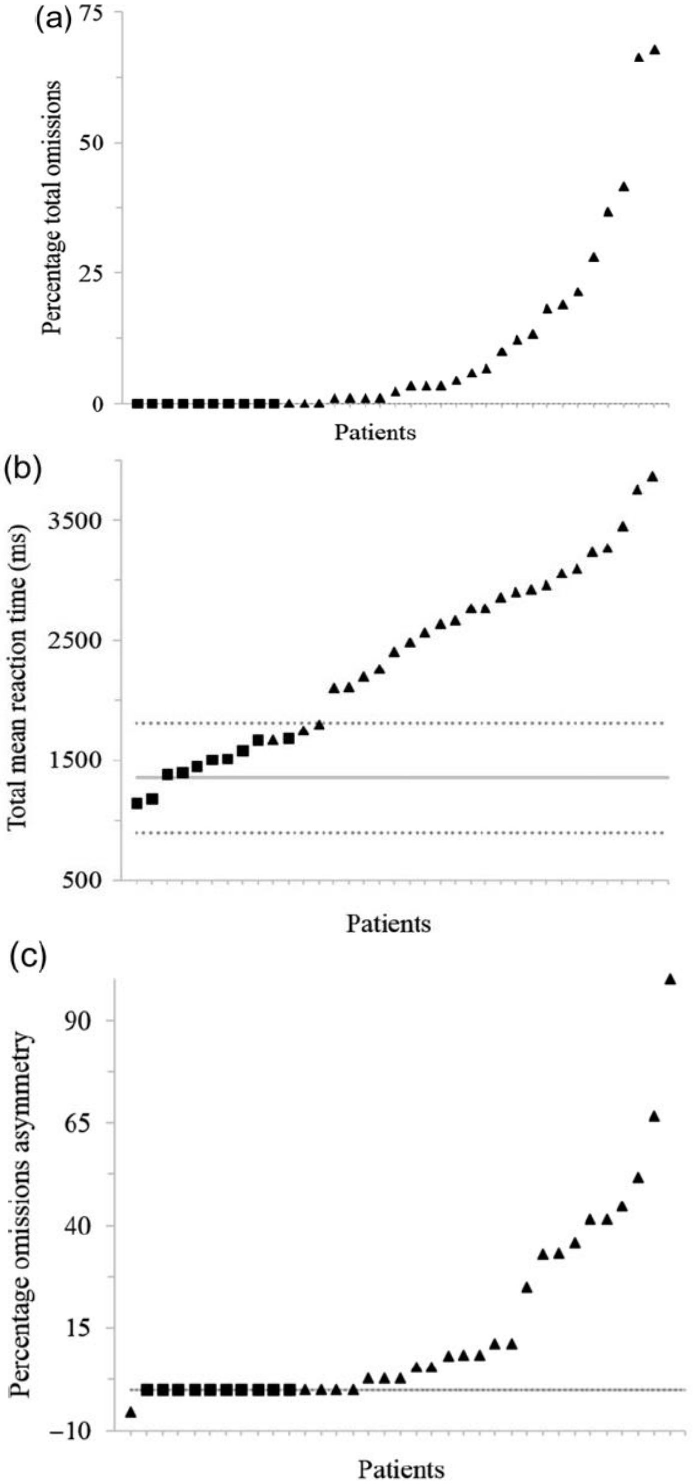
2.3 Results

Thirty-five brain-damaged patients (11 females) were included in the study. According to the clinical medical report, 23 patients had a right hemisphere lesion and 25 were diagnosed with egocentric hemineglect. All patients except one were right handed. All patients were between 41 and 85 years old [mean age (*SD*) = 62.63 (11.89)] and between 1 and 54 months post-onset [mean post-onset (*SD*) = 11.17 (12.30)] (see Table 1 for precise details). Fifty-six healthy control participants were tested (38 females and seven left handed; aged between 50 and 79 years, mean age (*SD*) = 62.6 (8.4). Healthy control participants and patients were paired by mean age (t (53.46) = .46, p= .64).

Table 1. Patients' demographic characteristics

No.	Gender	Age	Handedness	Lesion	Months post-onset	Paresis	Egocentric hemineglect
1	M	65	R	Right ischemic occipital and thalamic stroke	13	Yes	No
2	F	51	R	Right ischemic superficial middle cerebral vein stroke	12	Yes	Yes
3	M	64	R	Left hemorrhagic deep thalamic stroke	17	Yes	No
4	M	71	R	Right ischemic superficial middle cerebral vein stroke	35	Yes	Yes
5	M	62	R	Left ischemic cortico-frontal stroke	3	Yes	No
6	M	66	R	Right hemorrhagic fronto-parieto-temporal stroke	2	Yes	Yes
7	M	80	R	Left hemorrhagic internal capsule and thalamic stroke	2	Yes	No
8	M	41	R	Right hemorrhagic intracerebral lentiform nucleus and corona radiata stroke	54	Yes	Yes
9	M	48	R	Left ischemic frontal stroke	2	Yes	Yes
10	M	50	R	Right ischemic middle cerebral vein parieto-temporo-occipital stroke	13	Yes	Yes
11	M	48	R	Left hemorrhagic thalamic stroke	12	Yes	Yes
12	F	70	R	Right hemorrhagic occipital and thalamic stroke	6	Yes	Yes
13	M	66	R	Left hemorrhagic parieto-occipital stroke	18	No	Yes
14	F	45	R	Right hemorrhagic intracerebral lentiform nucleus and internal capsule stroke	1	Yes	Yes
15	M	84	R	Right ischemic middle cerebral vein stroke	5	Yes	Yes
16	F	71	R	Left hemorrhagic thalamic and internal capsule stroke	22	Yes	No
17	M	60	R	Left hemorrhagic fronto-temporal and basal ganglia stroke	9	Yes	No
18	F	72	R	Right hemorrhagic intracerebral fronto-parietal stroke	2	Yes	Yes
19	M	72	R	Right ischemic middle cerebral vein stroke	48	Yes	Yes
20	M	58	R	Right hemorrhagic middle cerebral vein stroke	14	Yes	No
21	F	47	R	Right hemorrhagic lentiform nucleus stroke	11	Yes	Yes
22	F	51	R	Left hemorrhagic subarachnoid intracerebral stroke	8	Yes	Yes
23	M	62	R	Right ischemic middle cerebral vein stroke	18	No	Yes
24	F	56	R	Right hemorrhagic central fissure stroke	12	Yes	No
25	F	72	R	Right hemorrhagic intracerebral parietal stroke	3	Yes	Yes
26	M	62	R	Right hemorrhagic fronto-parietal stroke	5	Yes	Yes
27	M	82	R	Right ischemic middle cerebral vein stroke	3	Yes	Yes
28	M	85	L	Right ischemic middle cerebral vein stroke	4	No	Yes
29	M	58	R	Left hemorrhagic thalamic and internal capsule stroke	8	Yes	Yes
30	M	53	R	Right ischemic middle cerebral vein stroke	11	Yes	Yes
31	M	53	R	Left ischemic middle cerebral vein and internal capsule stroke	5	Yes	No
32	M	65	R	Left ischemic lacunar stroke	2	Yes	No
33	M	68	R	Right hemorrhagic thalamic stroke	4	Yes	Yes
34	F	52	R	Right ischemic middle cerebral vein stroke	6	Yes	Yes
35	F	82	R	Right ischemic middle cerebral vein stroke	1	Yes	Yes

Note: M= male; F= female; R= right; L= left; paresis and egocentric hemineglect was determined by clinical neurological evaluation.


(a)
75
50
25
0
Percentage total omissions
Patients
(b)
3500
2500
1500
500
Total mean reaction time (ms)
Patients
(c)
90
65
40
15
−10
Percentage omissions asymmetry
Patients

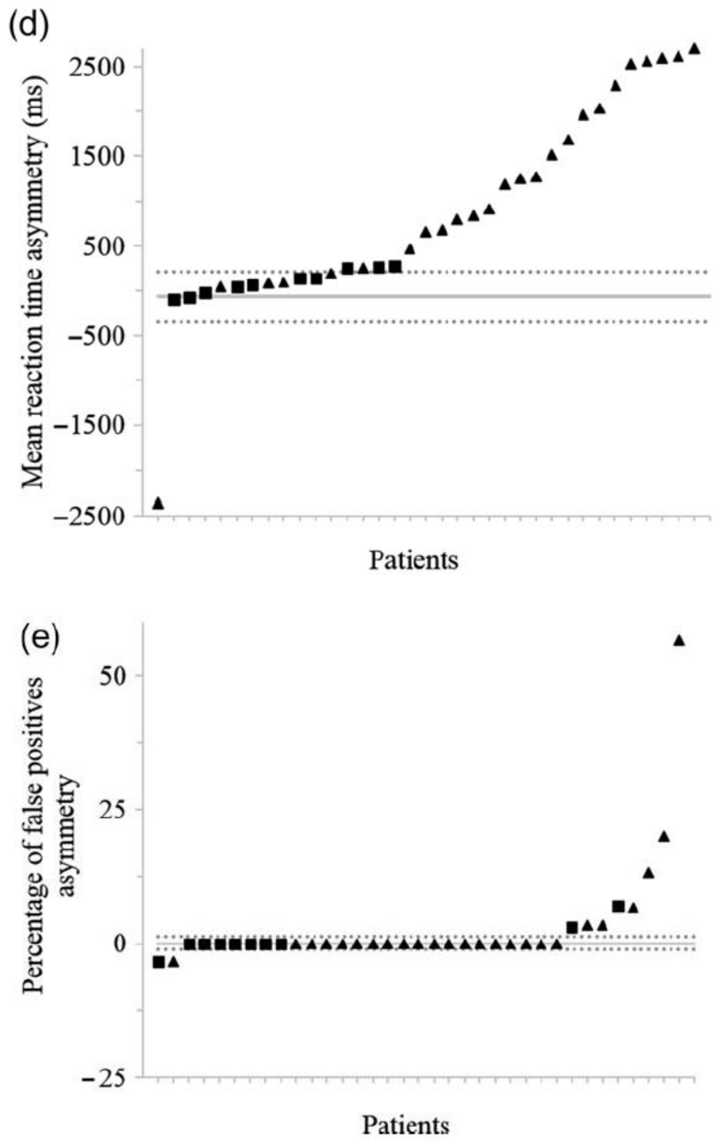


Figure 3. Individual egocentric hemineglect (determined by the clinical diagnosis; triangle) and hemiparesis without hemineglect (determined by the clinical diagnosis; square) patient responses to the MonAmour test relative to norms (mean full line, and 95% confidence interval dotted lines). The data points are organised by hemineglect severity respective to each measure at the MonAmour for: (a) percentage of total omissions, (b) total mean reaction time, (c) percentage of omissions asymmetry, (d) mean reaction time asymmetry, and (e) percentage of false positives asymmetry.

2.3.1 Normative data

The normative data were computed from the healthy participants' group (Figure 3). Note that healthy participants did not omit any targets, meaning that a single omission in patients was considered as an impairment. The norms created on the percentage of total omissions and on the total mean reaction time detected 22 out of 35 patients as having impaired overall performance (Figure 3a and b), though all 22 patients were also diagnosed as having egocentric hemineglect. Twenty-seven out of 35 patients were diagnosed as presenting egocentric hemineglect either on omission asymmetry or on mean reaction time asymmetry (Figure 3c and d). Note that one patient showed an inverse profile showing an important ipsilateral impairment on the mean reaction time asymmetry, and to a lesser extent on the percentage of omissions asymmetry. This behavior was also noted on the performance at the Apples and Neglect tests indicating an overcompensation of lateralised deficit. Norms on false positive asymmetry responses detected 10/35 patients with allocentric hemineglect (where 8/27 of patients showed egocentric hemineglect and only 2/35 patients showed exclusive allocentric hemineglect; Figure 3e). The remaining 6/35 patients showed no evidence of hemineglect at the MonAmour.

2.3.2 Criterion validity

Concerning the overall performance, percentage of total omissions on the MonAmour correlated strongly with the three standardised tests (Bells test: $r(33)= .88$, $p <.001$; Apples test: $r(33)= .78$, $p < .001$; Neglect subtest: $r(33)= .68$, $p < .001$). The total mean reaction time between the MonAmour and the Neglect subtest was also strongly correlated ($r(33) = .54$, $p < .001$). Compared to overall scores of the standardised tests, the MonAmour test was sensitive at 84% and specific at 54% (Table 2).

For egocentric hemineglect, moderate to strong correlations were found between the MonAmour and the standardised tests for the percentage of omissions asymmetry (Bells test: $r(33) = .70$, $p < .001$; Apples test: $r(33) = .69$, $p < .001$; Neglect Subtest: $r(33) = .40$; $p = .016$) and mean reaction time asymmetry (Neglect Subtest: $r(31) = .45$, $p = .008$; note that 2 patients made 100% omissions to contralesional targets meaning that there were no reaction time measures for these patients). Compared to the medical clinical diagnosis, results demonstrated that the egocentric component of the MonAmour test had a sensitivity of 96% and a specificity of 70%. With the standardised tests as reference, the MonAmour showed again a sensitivity of 96% and a slightly lower specificity of 58% (Table 2).

Regarding allocentric hemineglect, there was a strong correlation between the MonAmour test and the Apples test on the percentage of false positives asymmetry ($r(33) = .52$, $p < .001$). Comparing the patients diagnosed with allocentric hemineglect on the MonAmour and on the Apples test, results showed a sensitivity of 50% and specificity of 77% (Table 2).

Table 2. Patients diagnosed as impaired for the MonAmour and the standardised clinical diagnosis tests.

	MonAmour test	Bells test	Apples test	Neglect test
Egocentric hemineglect				
Percentage omissions asymmetry	21	10	11	15
Mean reaction time asymmetry	24	/	/	18
Allocentric hemineglect				
Percentage false positives asymmetry	10	/	8	/
Overall performance				
Percentage total omissions	22	9	13	13
Total mean reaction time	22	/	/	5

Note: / = not applicable.

2.3.3 Reliability

The test-retest ICC analyses of overall attention performance was excellent both for the percentage of total omissions (ICC = .95, p <.001) and total mean reaction time (ICC = .95, p <.001). The reliability of egocentric hemineglect showed excellent reliability for the percentage of omissions asymmetry (ICC = .94, p < .001), and the mean reaction time asymmetry (ICC = .79, p < .001). However, the reliability of allocentric hemineglect showed non-significant results for the percentage of false positives asymmetry (ICC = -0.13, p = .512).

The MDC showed that to demonstrate a pre- versus post- improvement of patients' performance with the MonAmour, a difference of at least 5% on percentage of total omissions, 370 ms on total mean reaction time, 13% on percentage of omissions asymmetry and 1202 ms on mean reaction time asymmetry is needed. The MDC of the percentage of false positives asymmetry could not be calculated as the ICC for this variable was not significant.

2.4 Discussion

In daily clinical routine, time constraints prevent clinicians from administering extensive and complete batteries of assessments, and instead, they are forced to select some tests, and miss the evaluation of some cognitive functions (Grattan & Woodbury, 2017; Petzold et al., 2014). Moreover, literature has reported a lack of sensitivity of paper and pencil tests (Bonato, 2012; Buxbaum et al., 2012). These issues motivated the development of a new and innovative robot assessment, the

MonAmour test developed on the REAplan® robot (though it should be noted that it could be implemented on other robots). As in recent VR assessments (e.g., Fordell et al., 2011; Tanaka et al., 2010), the MonAmour test was based on standardised tests (e.g., the Apples test). These innovations provide additional sensitive measures compared to paper and pencil tests (e.g., reaction time responses), allow for a standardised administration between clinicians (thereby reducing errors), and diminish learning effect (e.g., target position randomization). Specifically, the MonAmour measures movement kinematics, provides clinicians with immediate results compared to norms and allows for the combined evaluation of three different forms of hemineglect. In the present paper, the aim was to validate the egocentric and allocentric assessments of the MonAmour test.

Comparing our patients to the norms, we found evidence of patients having egocentric and allocentric forms of hemineglect, with patients showing egocentric and not allocentric hemineglect, and two patients showing allocentric and not egocentric hemineglect. This independence between forms of hemineglect replicates previous behavioral (Bickerton et al., 2011) and neuroimaging findings (Medina et al., 2009). The validation of the egocentric and allocentric components of the MonAmour was tested by comparing the results of the patients on the MonAmour test with three standardised assessments of hemineglect; the Bells test, the Apples test and the Neglect test from the TAP. Patients' performance for egocentric hemineglect at the MonAmour was highly correlated with patients' performance on the standardised tests for omissions asymmetry and mean reaction time asymmetry. The egocentric sensitivity of the MonAmour test was excellent, showing the capacity to include patient presenting hemineglect with greater sensitivity than some recently published tests such as the VRLAT (56% sensitivity; Buxbaum et al., 2012) and the VR-DiSTRO (33% sensitivity for the VR lines bisection test and 54% sensitivity for the VR stars cancellation test; Fordell et al., 2011). Specificity of the MonAmour was good at excluding patients without hemineglect when using the clinical diagnosis criteria as reference. However, specificity rate was lower (though still good) when using the standardised tests diagnosis. This may be explained by a practice effect on the standardised tests. For the MonAmour test, the diagnosis of hemineglect remained stable, possibly due to the use of randomized target and distractors positions, and because the MonAmour uses combined measures of omission and reaction measures making the test more precise. This is consistent with the finding that the MonAmour detected more patients with impairments than standardised tests (Table 2). Finally, test-retest reliability was excellent and minimal detectable change was established for future use of the test with the aim to assess patients' improvement (e.g., pre/post-treatment).

As well as showing validation of egocentric measures of hemineglect, the present results also demonstrated the validation of the allocentric part of the MonAmour with the allocentric measure of the Apples test (Bickerton et al., 2011). The correlations between both tests were strong. However, the reliability of the false positives asymmetry was non-significant. This null result can be partially explained by the low prevalence of allocentric relative to egocentric hemineglect (Bickerton et al., 2011). Further, we recruited patients based on the presence (or absence) of egocentric hemineglect, as allocentric hemineglect was not systematically tested in clinics where we recruited the patients. As a consequence, only a few of our patients showed allocentric hemineglect, often exhibiting mostly slight impairments (see Figure 3e for the severity of allocentric impairment in our sample). Results showed a weak sensitivity but a good specificity. Several arguments could explain this low sensitivity. Firstly, our sample contained only three patients showing severe allocentric hemineglect (with all three detected as impaired on both the MonAmour and Apples tests). Secondly, the low sensitivity might be explained by the definition of false positives that we used to calculate allocentric hemineglect in the MonAmour test. We defined false positive responses as an error on incomplete target trials where the participant pushed the end-effector as if the target was complete. However, false positive errors on complete target trials, where the participant pulled the end-effector as if the target was incomplete might also be considered as a measure of allocentric hemineglect. In this case, we could suggest that participants with allocentric hemineglect neglected the contralateral part of the complete target. This raises an interesting question about whether there may be different forms of allocentric hemineglect, or at least differences in the way in which allocentric hemineglect is evaluated and defined. Thirdly, there could be differences caused by the tasks. In the Apples test, participants have to detect the correct target (complete target). In the MonAmour, participants have to discriminate the targets (complete or incomplete) and make a choice-response (push or pull the handle). Since the discrimination takes more time than detection (Van der Lubbe, Vogel, & Postma, 2005), it could lead to a more conscious processing of the target, and to a different pattern of responses. Finally, we only compared the allocentric component of the MonAmour with the Apples test because it is the only clinically objective quantitative test for allocentric hemineglect. This raises two concerns. As recommended by Basagni and colleagues (2017) and Azouvi and colleagues (2002), one test is not enough to establish the true presence or absence of deficits. Moreover, the Apples test's allocentric sensitivity/specificity has never been established, therefore putting the present results into perspective.

In our evaluation, we considered asymmetric measures in order to reduce the chances that a clinician makes a false diagnosis of a patient who is equally impaired in both contralesional and ipsilesional space. However, this may cause us to fail to measure overall attentional impairment not related to hemineglect, especially as several studies have highlighted that non-lateralised deficits can occur in addition to hemineglect, and can even exacerbate it (Husain & Rorden, 2003). To solve this problem, we considered overall performance measures related to non-spatial impairments. Overall performance strongly correlated between the MonAmour and the standardised tests, with results showing high sensitivity and reliability. Overall performance demonstrated an impairment in 22 patients of our sample, in addition to their egocentric hemineglect deficit. Moreover, it showed that five patients had overall impairments without egocentric asymmetric deficit. This highlights the importance of combining asymmetric measures to overall performance measures for more depth in the assessment, and for a more adapted rehabilitation to the patients' deficits.

Within the scope of our study, our aim was to investigate asymmetric impairments in the contralesional hemispace independently of the patients' lesion side. For more specific results, detailed brain imaging could be used to refine the diagnosis of the patients especially since studies have shown that lesion side, site and size can impact the severity of hemineglect and the presence of additional non-lateralised deficits (Husain & Rorden, 2003). Similarly, as part of this study, hemianopia was not systematically assessed since participants were allowed to make eye and head movements in space exploration while performing the tests. In order to confirm any influence of hemianopia on patient's performance, the use of eye-tracker measures could be added to the testing (Tsirlin, Dupierrix, Chokron, Coquillart, & Ohlmann, 2009).

Future studies will include a larger sample of patients in order to confirm the validity of the egocentric and allocentric components of the MonAmour. Furthermore, we will deepen the assessment and understanding of the different forms of hemineglect. These investigations will consist of two related tracks. Firstly, in current clinical assessment of hemineglect, frequently, paper and pencil tests are completed with the ipsilesional hand. This is partially due to the definition that hemineglect should not be caused by motor deficits (Heilman et al., 2000) such as hemiparesis that frequently co-exists with hemineglect (Jehkonen et al., 2000; Jehkonen et al., 2006). However, the definition of hemineglect would be better understood if both the non-hemiparetic and hemiparetic hands were included in the assessment. Future studies will therefore administer the MonAmour with both hands (if possible; i.e., in patients without hemiplegia), to investigate the common features of hemineglect across the two hands. Secondly, we will integrate the action component of the MonAmour test. Instead of pulling or pushing the end-effector of the robot to make a response, patients will be asked to reach to the target when it is complete, versus reach to the musical stand when it is incomplete. Importantly, the robot will measure different aspects of the action, including movement time, speed, smoothness, straightness and accuracy. As in the current version of the task, these measures will be analysed online and the results will be compared to the norms giving instant results to the clinician. Administrating this action version of the MonAmour in addition to the original perception version of the MonAmour presented here will allow a thorough investigation of differences between perception and action in hemineglect, and allow the comparison of patients' performance in contrast to control hemiparesis patients (without hemineglect) and healthy participants. This will lead to a highly accurate assessment of different forms of hemineglect (acute to late post-stroke patients), improving the ability to plan a rehabilitation program tightly linked to the patients' performance and facilitating faster recovery.

Chapter 3

Upper limb action kinematics in egocentric hemineglect

Chapter 3

Upper limb action kinematics in egocentric hemineglect

Abstract

Objective: The aim of the study was to investigate visually guided reaching action kinematics towards contralesional versus ipsilesional hemispace in patients with left egocentric hemineglect compared to healthy control participants, manipulating visual attentional load and hand used. **Methods:** We tested eleven right stroke patients presenting egocentric hemineglect and forty-eight healthy control participants. In Experiment 1, participants were required to perform two target reaching tasks on a robot device, one with and one without attentional load. Patients performed the tasks with their ipsilesional hand and healthy control participants with their dominant hand. The measured variables were reaction time, execution time, peak speed, smoothness, straightness and accuracy. In Experiment 2, a subset of patients without hemiplegia and healthy control participants performed the target reaching task, but this time only the version with attentional load, and now comparing performance of the ipsilesional/dominant hand to the contralesional/non-dominant hand. **Results:** Compared to healthy control participants, reaction time in egocentric hemineglect patients showed a lateralised effect towards contralesional compared to ipsilesional hemispace for both hands, with increased impairment with attentional load. However, action execution kinematics did not demonstrate any asymmetry for contralesional compared to ipsilesional hemispace. **Conclusions:** In hemineglect patients, reaction time demonstrated a contralesional bias increased by the attentional load condition, whereas the action execution kinematics did not show a spatial impairment. Results are discussed in terms of the planning-control model.

3.1 Introduction

Hemineglect refers to the inability to process or react to stimuli that are presented in the hemispace contralateral to a brain lesion (Heilman et al., 2000). Although perception features of hemineglect are well defined (e.g., egocentric or allocentric viewpoint; Kerkhoff, 2001), the literature of hemineglect demonstrates lots of mixed results for action kinematics (i.e., temporal and spatial characteristics of an action).

There are several reports of impaired visually guided action kinematics made by hemineglect patients with their ipsilesional hand. These action kinematics are reported to be impaired when made towards or in contralesional hemispace compared to towards or in ipsilesional hemispace (Coulthard et al., 2006; Harvey & Rossit, 2012; Heilman et al., 2000). For example, some authors required that hemineglect patients moved to a wooden handle placed on a horizontal metal track and showed slower reaction time for contralesional actions (Heilman et al., 1985). Similarly, another group of researchers tested the actions of hemineglect patients on a task requiring six consecutive actions on two columns of targets, alternating rightward and leftward actions (Mattingley et al., 1994). Their results showed slow reaction time, execution time, time to peak velocity, time spent in force production and more jerkiness for contralesional compared to ipsilesional movements (see Mattingley, Bradshaw, & Phillips, 1992 for similar results). Additionally, the authors observed that for contralesional movements, patients frequently undershot the target position. In these papers, either the direction of the action or the location of the target seemed to cause a change in the movement kinematics.

Other authors used a paradigm dissociating the target location from the direction of the reaching action on a horizontal apparatus (Husain et al., 2000). Hemineglect patients were asked to reach to a target placed in the contralesional hemifield, performing either an action towards the contralesional side (e.g., starting position at the right of the target) or an action towards the ipsilesional side (e.g., starting position at the left of the target). They found that hemineglect patients reached more slowly to targets located in the contralesional than ipsilesional hemifield. Additionally, reaction time for targets in the contralesional hemifield were significantly less impaired when ipsilesional actions were required. These results suggest that the effects of hemineglect on actions could be explained by the intended action direction of response to a target rather than by the target location relative to the body. This effect was supported by Bartolomeo et al. (2001), who developed a perceptual task where patients made central responses to lateralised targets (i.e., left, centre or right) and a motor task requiring lateralised responses (i.e., left or right side of a keyboard) for vertical central targets. Like Husain et al. (2000), results for the motor task demonstrated that hemineglect patients were systematically slower when performing contralesional compared to ipsilesional hand movements to respond to centralized (non-lateralised) targets.

In contrast to these papers, other research showed that hemineglect may influence differently perception and action responses, whereby only perception responses demonstrate a lateralised bias towards the contralesional hemifield, and action remains unaffected. For example, Karnath, Dick, and Konczak (1997) asked patients to perform 3D pointing movements to three LED's (i.e., one aligned to the participant's sagittal trunk, and two others aligned with their left and right shoulder), with the starting position located in the ipsilesional hemispace. No difference was found between hemineglect patients, patients without hemineglect and healthy control participants for measures of terminal accuracy (i.e., distance between the target and the tip of the index finger at the end of the movement) and direction-specific deviation from a straight line hand path. These results lead to the authors concluding that hemineglect had no specific influence on action (see Himmelbach & Karnath, 2003 for similar results). These results were in contrast to Mattingley et al. (1994), but could arguably be caused by the choice of kinematic measures. However, Konczak and Karnath (1998) investigated hand velocity in hemineglect patients using the same paradigm as in the previous study (Karnath et al., 1997), but this time measuring peak velocity, time to peak, time from peak velocity, and total movement time. Their results demonstrated a global slowness in movement execution and reduced peak velocity relative to healthy control participants, but no significant difference from brain-damaged patients without hemineglect, and no directional bias (see Farnè et al., 2003; Rossit, Muir et al., 2009 for similar results).

Despite these several attempts trying to define visually guided action impairments in hemineglect, results in the literature remain mixed. This lack of consensus partly stems from the large variety of variables investigated (e.g., reaction time, hand path, peak speed), the variety in paradigms, exploring either directional movement (i.e., movements towards the contralesional or ipsilesional hemispace regardless of the hemispace where the movement takes place) or spatial movement (i.e., movements in the contralesional or ipsilesional hemispace regardless of the direction of the movement), and the heterogeneity in the type of patients tested (e.g., lesion site and side).

In the present paper, the aim of Experiment 1 was to investigate whether reaching action kinematics towards the contralesional versus ipsilesional hemispace in left egocentric hemineglect patients would differ from healthy control participants. This aim was investigated using two target search tasks manipulating attentional load. We hypothesized that in contrast to healthy control participants, actions kinematics in hemineglect patients would demonstrate a lateralised bias when reaching towards contralesional and extreme contralesional hemispace relative to ipsilesional and extreme ipsilesional hemispace. As attentional load has been demonstrated to moderate perceptual hemineglect (Bonato & Cutini, 2016; Kaplan et al., 1991), we predicted that attentional load would also moderate action kinematics impairments in hemineglect patients, with greater deficits in the task with than without attentional load. In Experiment 2 of this paper, the aim was to compare, in a subset of hemineglect patients without hemiplegia and in healthy control participants, action kinematics of both hands, without considering absolute hand impairment. Since the starting position was identical for both hands (i.e., patient's body midline), we hypothesized no difference between hands, with both hands showing lateralised action kinematics towards the contralesional compared to ipsilesional hemispace for hemineglect patients, and no difference in laterality for control participants.

3.2 Methods

3.2.1 Participants

Brain-damaged participants were recruited using a consecutive sampling. The inclusion criteria included having a first right ischemic or haemorrhagic unilateral stroke, a clinical diagnosis of hemineglect (e.g., paper and pencil tests such as the Bells Test), an egocentric impairment at the pushing version of the MonAmour test (Montedoro et al., 2018; Chapter 2) at the time of the testing, a sufficient comprehension of the task instructions, the ability to move the end-effector of the REAplan® robot voluntarily and right handedness. The exclusion criteria were orthopaedic illness limiting upper limb function, and the diagnosis of neurodegenerative disease or any other neurological conditions. Patients were recruited from the neuropsychological, and physical medicine and rehabilitation departments of the Cliniques universitaires Saint-Luc, and from the Centre Hospitalier Neurologique William Lennox in Belgium. Healthy control participants were selected with the criteria of being free of neurological illness, having good understanding of the instructions, and being right handed. All participants participated voluntarily to the study and gave their written formal consent. The study was approved by the Saint-Luc Biomedical Hospital-Faculty Ethics Committee and the protocol was registered at ClinicalTrials.gov (NCT02543424).

In Experiment 1, eleven right stroke hemineglect patients were included in the study (Table 1 & 2). From this hemineglect group, a sub-group of four patients was created for Experiment 2, which consisted of hemineglect patients without hemiplegia (Table 1 & 2). Forty-eight healthy control participants participated to the study (Table 1). The main group of hemineglect patients and healthy control participants did not differ in mean age ($t(57)=1.6$, $p= .12$). However, the mean age of the hemineglect sub-group was different from healthy control participants ($t(50)=2.7$, $p= .008$). Participants' handedness was confirmed by the Edinburgh Handedness Inventory (Oldfield, 1971).

Table 1. Demographic characteristics of the participant groups.

	Hemineglect patients [a] (n = 11)	Hemineglect patients without hemiplegia [b] (n = 4)	Healthy control participants (n = 48)
Age (years), mean (SD)	66.8 (12)	73.7 (7)	62.1 (8.2)
Sex (male/female), n	7/5	4/0	17/31
Time post stroke (months), mean (SD)	12.1 (15.1)	23 (22)	NA

Note: NA= not applicable; [a] Patient group used in Experiment 1; [b] Patient group used in Experiment 2.

Table 2. Detailed demographic characteristics of the patients.

N°	Gender	Age	Lesion	Months post-onset	Upper limb weakness
1*	M	68	Right haemorrhagic thalamic stroke	4	HP
2*	M	71	Right ischemic superficial middle cerebral artery stroke	35	HP
3*	M	72	Right ischemic middle cerebral artery stroke	48	HP
4*	M	84	Right ischemic middle cerebral artery stroke	5	HP
5	F	47	Right haemorrhagic lentiform nucleus stroke	11	HPL
6	F	52	Right ischemic middle cerebral artery stroke	6	HPL
7	M	53	Right ischemic middle cerebral artery stroke	11	HPL
8	M	62	Right haemorrhagic fronto-parietal stroke	5	HPL
9	F	72	Right haemorrhagic intracerebral fronto-parietal stroke	2	HPL
10	F	72	Right haemorrhagic intracerebral parietal stroke	3	HPL
11	M	82	Right ischemic middle cerebral artery stroke	3	HPL

Note: M= male; F= female; HP= hemiparesis; HPL= hemiplegia; *= Patients that did Experiment 1 and 2.

3.2.2 Materials

3.2.2.1 Apparatus

The Axinesis REAplan® end-effector robot (Figure 1) was used to measure upper limb movements in the horizontal plane (93 x 52 cm). The participants made responses to targets presented on a monitor (1920 x 1080 pixels; scale 1:1) placed in front of them. A separate monitor for the experimenter was located next to the horizontal plane in order to plan the exercises and follow participant performance. Position and force captors in the handle of the robot allowed for precise measurements of the action kinematics (125 Hz). In the present study, the robot was used in the active mode, where no assistance was provided by the robot during movements to measure the actual performance of the participant's action responses.

3.2.2.2 Range of motion task

Prior to the initiation of the MonAmour and control reaching tests (see description below), a range of motion task was performed to calibrate the area of the REAplan® horizontal plane in which the participant was able to reach. Participants were asked to grip the end-effector with their hand, and actively reach (without help and compensatory movements) the maximum surface of the plane. The task was performed with both hands (one at a time), except in patients presenting hemiplegia. If the participant could reach the entire horizontal plane, the scale between the plane and the screen displaying the MonAmour and the control reaching tests remained 1:1. However, if the participant could only reach parts of the horizontal plane, the scale between the plane and the screen displaying the tests was adjusted so that the correspondence between the hand and target was reduced (e.g., 1:0.5), allowing the participant to reach to all the targets presented on the screen with less action distance. The scaling was linear, such that left versus right targets were always placed at the same distance. For the participants who performed the MonAmour with both hands (Experiment 2), the same scale was used for both hands (i.e., using the smallest range of motion of the two).

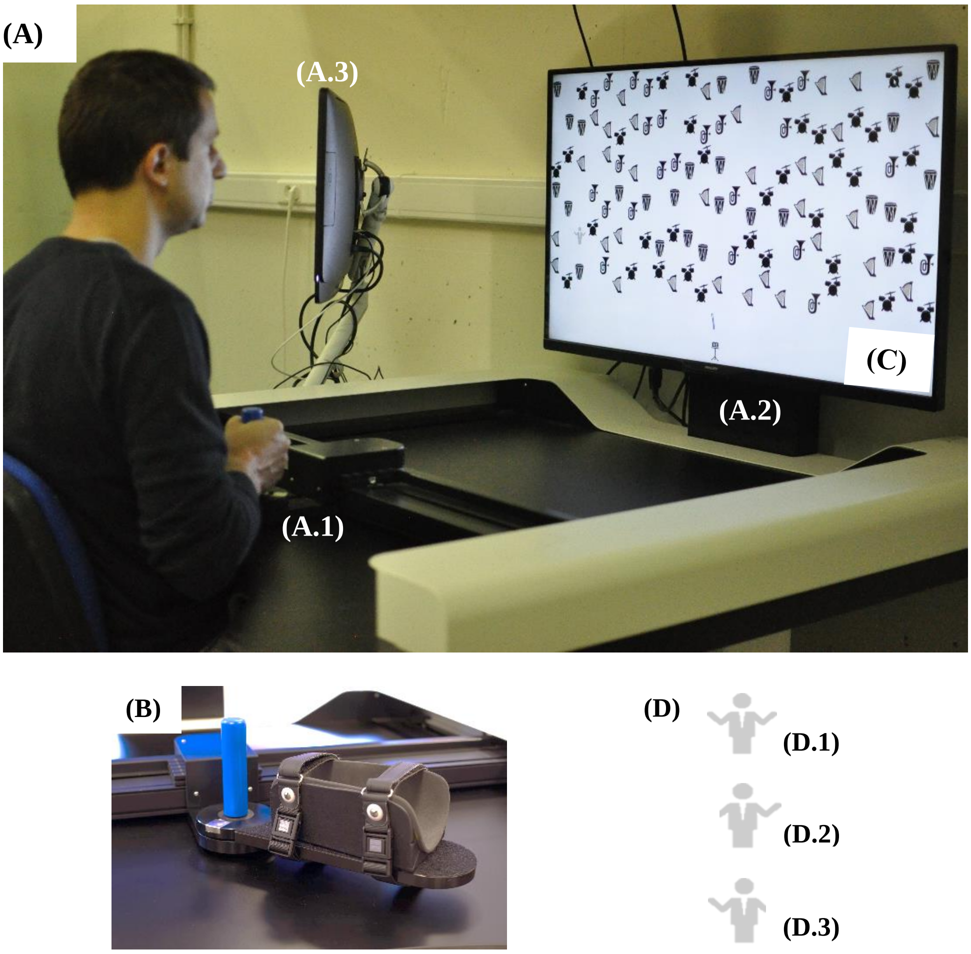


Figure 1. The REAplan® robotic device and the MonAmour test. (A) The robotic device incorporates: (1) an end-effector with position and force sensors, (2) a monitor for the participant and, (3) a monitor for the experimenter; (B) The forearm gutter that can be used to stabilise the participant's arm (Copyright 2018 by Axinesis, reprinted with permission); (C) The MonAmour reaching test; (D) Types of target in the MonAmour test: (1) the complete target, (2) the left-incomplete target, (3) the right-incomplete target.

3.2.2.3 MonAmour reaching test (attentional load condition)

The MonAmour reaching test (Figure 1) used in the present study was similar to that presented in Montedoro et al. (2018) (Chapter 2). It was a target search task where participants were asked to detect a musical conductor (i.e., the target) among musical instruments of four different types (i.e., the distractors; corresponding to attentional load). Three different types of target were included in the test (Figure 1): complete targets (i.e., a musical conductor with two arms; to measure egocentric hemineglect) and right or left-incomplete targets (i.e., a musical conductor with a right or left arm missing; to measure allocentric hemineglect). Target and distractors were organized in an invisible grid of 30 cells (5 columns x 6 rows). Ninety trials were presented with 29 cells containing four distractors randomly organised, and 1 cell containing three distractors and the target. The target always presented in the centre of the cell. Each type of target was randomly placed in each of the 30 cells (thirty trials per type of targets). Ten catch trials without target were included in the test in order to detect impulsive responses or misunderstanding of the instructions.

The only difference with the pushing version of the MonAmour test (Montedoro et al., 2018; Chapter 2) and the current reaching version of the test was that participants made a reaching response, instead of a pushing response. The trial started with a fixation cross (1500 ms). Following the fixation cross, a target and the distractors were presented. The starting position was centred at the bottom of the screen between the musical stand and the musical instruments, aligned with the participant's body midline (Figure 1). If the musical conductor target was complete, participants were asked to reach to the target by moving the end-effector of the robot as direct as possible. If the musical conductor was incomplete, participants were asked to reach the musical stand by moving the end-effector of the robot. For each movement of the end-effector, the baton on the screen indicated the position of the acting hand. For catch trials, participants were instructed to make no response. Participants had maximum 7000 ms to initiate the movement towards the target, which had to be reached within a maximum of 20000 ms (i.e., correct response). The response movement had to stay within the boundaries of a virtual corridor of 7000 mm width connecting the starting and target position, thus controlling the direction of the participant's movement towards the target. If no response was made after 7000 ms (i.e., omission response), or if the response movement was not made within the virtual corridor (i.e., the response was made towards a distractor; error response), the trial ended. At the end of a trial, the robot end-effector automatically returned to the starting position and the next trial was initiated. The virtual corridor was implemented to avoid that participants would find the target by chance by performing exploratory movements on the horizontal plane. The theoretical total test duration ranged from 10 to 33 minutes (with an approximate duration of 15 minutes for a hemineglect patient omitting all the contralesional targets). Instructions and training trials were performed before the beginning of the measurement.

3.2.2.4 Control reaching test (no attentional load condition)

The control reaching test was similar to the MonAmour reaching test (see description above), except that the trials were presented without any distractors (no attentional load) and only with complete targets. Therefore, thirty trials were presented with one target per trial randomly displayed across the 30 cells of the invisible grid. As for the MonAmour reaching test, patients were instructed to search for the target on the screen and then reach to it as directly as possible. The theoretical total test duration ranged from 3 to 10 minutes (with an approximate duration of 5 minutes for a hemineglect patient omitting all the contralesional targets).

3.2.3 Procedure

The testing was conducted in two sessions (separated by to 2 to 5 days). The sessions involved the range of motion task and then either the MonAmour reaching test (with attentional load) or the control reaching test (without attentional load), counterbalanced between participants. Healthy control participants performed both reaching tests with their dominant hand and all the patients used their ipsilesional hand (Experiment 1). Additionally, healthy control participants and patients without hemiplegia (Table 1 & 2) performed the MonAmour reaching test with their non-dominant/contralesional hand (Experiment 2). Hand order was counterbalanced between participants. Breaks were possible at any time during the sessions.

The position of the participants was standardised during the testing. They were placed in the middle of the horizontal plane of the REAplan®, in front of the participant screen (i.e., 52 cm; visual angle of 84°). The height of the robot's horizontal plane was adjusted to the participant's height. When necessary, their feet were placed on a footrest to ensure stability. The participants' trunk was held to the back of the chair, reducing compensatory movements. The participant's forearm was fixed into a gutter support attached to the end-effector to ensure wrist and forearm stability (especially for testing the contralesional hand, ensuring that participants performed the movements with all the hand and not just the fingers tips; Figure 1). Eye and head movements were unrestricted to allow participants with potential visual field deficits to perceive the target across the contralesional and ipsilesional space. The tests were either administrated in a laboratory at the Université catholique de Louvain or in one of the two hospitals where the patients were recruited.

3.2.4 Data analyses

The action kinematic variables were: (1) reaction time (i.e., time between the disappearance of the fixation cross and the participant's initiation of the movement; ms); (2) execution time (i.e., time between first movement in the direction of the target and target acquisition; ms); (3) peak speed (i.e., maximal speed; cm/s); (4) straightness (i.e., relation between the distance separating the starting position and target relative to the path length covered by the participant, with ratios close to 1 indicating more rectilinear movements); (5) smoothness (i.e., relation between mean and peak speed, with ratios close to 1 indicating smoother movements); and (6) accuracy (i.e., distance between the position of the end-effector at the end of the trial and the centre of the target, with higher scores indicating less accurate movements; mm). Straightness and smoothness measures on the REAplan® have been validated (Gilliaux et al., 2014).

Left and right space were redefined in terms of contralesional and ipsilesional space. As described above, hidden within the tests, there were five invisible columns with each column having six targets locations (one per row). This independent variable was labelled as “Distance-x” with 0 = extreme contralesional column; 20 = contralesional column; 40 = central column; 60 = ipsilesional column; and 80 = extreme ipsilesional column. In Experiment 1, action kinematics of the ipsilesional hand for patients and dominant hand for heathy controls were analysed between Groups (i.e., hemineglect patients vs. healthy control participants), Distance-x (i.e., 0, 20, 40, 60, 80), and Tasks (i.e., MonAmour vs. control reaching tests). In Experiment 2, only the action kinematic variables showing significant lateralised effects in Experiment 1 were analysed, between Groups (i.e., hemineglect patients without hemiplegia vs. healthy control participants), Distance-x (i.e., 0, 20, 40, 60, 80), and Hands (ipsilesional for patient and dominant for healthy control participants vs. contralesional for patients and non-dominant for healthy control participants), using only the MonAmour reaching test.

Data were analysed using SPSS software (IBM, SPSS statistics 25). Within the scope of this paper, only trials to complete targets (i.e., reaching the musical conductor; Figure 1) were analysed since the reaching actions for incomplete targets (i.e., reaching the musical stand) were too short to investigate action kinematics. Reaction time and execution time data were transformed in natural logarithm (ln) to obtain normal distributions. In Experiment 1, a generalized linear mixed model was used for all the dependent variables with Group, Distance-x, Task and their interactions as fixed effects, and Participants as a random factor. In Experiment 2, a generalized linear mixed model was used with Group, Distance-x, Hand and their interactions as fixed effects, and Participants as a random factor. For post-hoc analysis, sequential Bonferroni correction were used in pairwise comparisons ($p < .05$). For the pairwise comparisons of the significant main effects, the Mean (M) and Standard Error (SE) were reported.

3.3 Results

3.3.1 Experiment 1

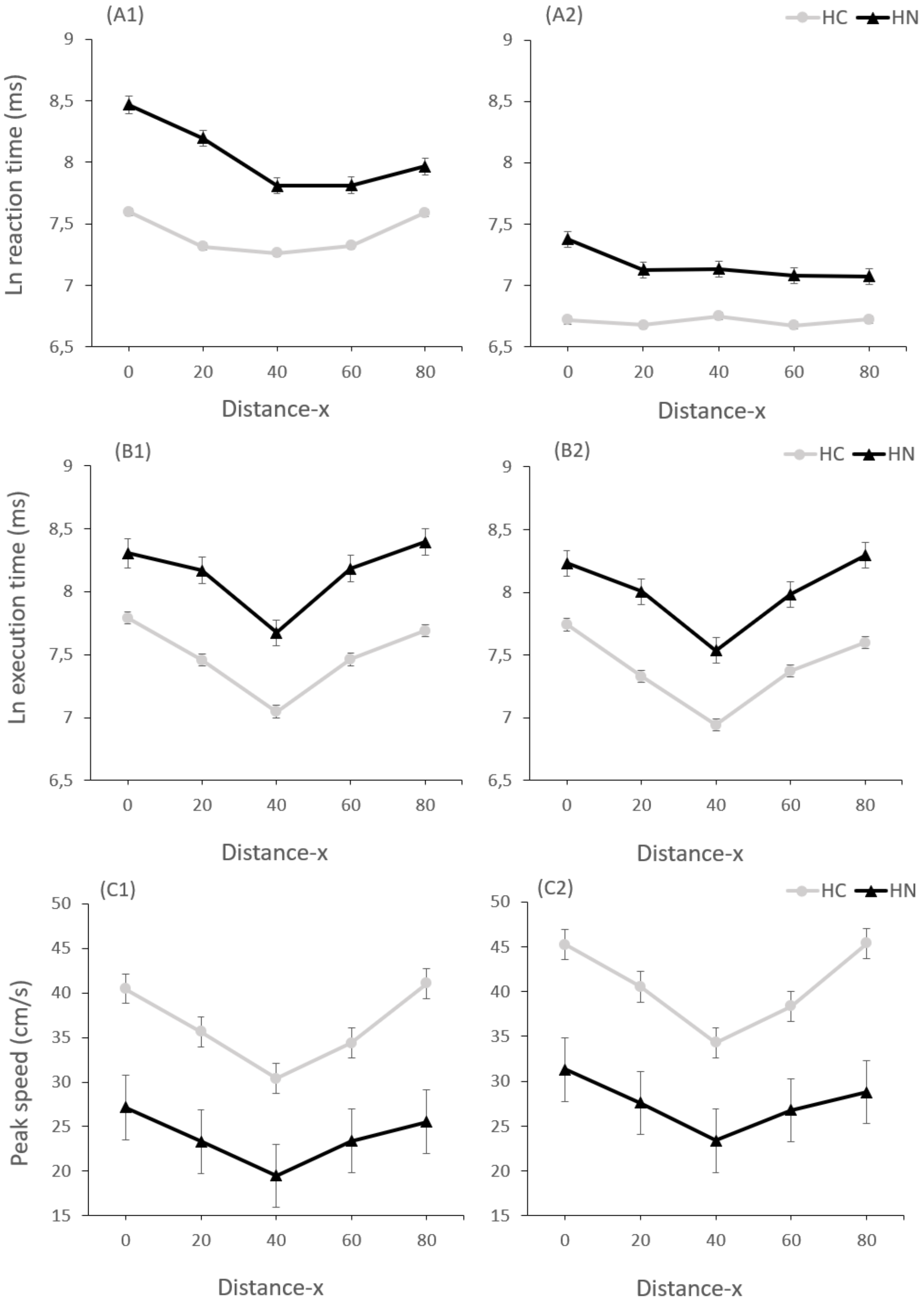
Only correct responses to complete targets (i.e., trials where the participants reached the target within the virtual corridor in maximum 20000 ms) were included (healthy control participants: 99.7% at MonAmour reaching test, 99.6% at the control reaching test; hemineglect patients: 80.7% at the MonAmour reaching test, 91.2% at the control reaching test).

Analysis of ln reaction time (Figure 2) showed a main effect of Group ($F(1, 3.4)= 80.2$, $p<.001$), where the hemineglect patients (M= 7.6, SE= 0.06) were significantly slower to initiate action than the healthy control participants (M= 7.1, SE= 0.03). The analysis also showed a main effect of Distance-x ($F(4, 3.4)= 65.2$, $p<.001$). Pairwise comparisons showed significant differences between all distances, except between 20 and 80, and between 40 and 60 (distances 0: M= 7.5, SE= 0.03; 20: M= 7.3, SE= 0.03; 40: M= 7.2, SE= 0.03; 60: M=7.2, SE= 0.03; 80: M= 7.3, SE= 0.03). A main effect of Task ($F(1, 3.4)= 3579.3$, $p<.001$) showed quicker reaction for the control (M= 6.9, SE= 0.03) than the MonAmour reaching tests (M= 7.7, SE=0.03). Results showed a significant Group by Distance-x interaction ($F(4, 3.4)= 29.4$, $p<.001$). For healthy control participants, distance 0 and 80 were not different from one another, but distance 0 and 80 were significantly slower than all other distances. For the hemineglect patients, all the distances were significantly different from one another, except between distances 40 and 60, 40 and 80, and 60 and 80. The Group by Task interaction was significant ($F(1, 3.4)= 45.9$, $p< .001$). For both groups, the reaction time for the control reaching test was significantly quicker than the MonAmour reaching test. The Distance-x by Task ($F(4, 3.4)= 27.4$, $p< .001$) was also significant, where for the MonAmour reaching test, all distances were significantly different from one another, except between distances 20 and 80, and 40 and 60. Instead, for the control reaching test, only distance 0 was significantly slower than all other distances. Finally, the triple interaction was significant ($F(4, 3.4)= 7.2$, $p< .001$). For healthy control participants in the MonAmour reaching test, the reaction time at distance 0 and 80 was significantly different from all the other distances, but not different from one another. For healthy control participants in the control test, only distance 40 was significantly slower than 20 and 60. For the hemineglect patients in the MonAmour reaching test, all distances were significantly different from one another (including distance 0 compared to 80 and 20 compared to 60), with the exception of distance 40 and 60. For the hemineglect patients in the control reaching test, only distance 0 was significantly slower than all the other distances. For all distances, and for both tasks, healthy control participants were significantly quicker than hemineglect patients.

Ln execution time analysis (Figure 2) demonstrated a main effect of Group ($F(1, 3.4)= 41.9$, $p< .001$), where healthy control participants were significantly quicker

(M= 7.4, SE= 0.04) than hemineglect patients (M= 8, SE= 0.09). Results also demonstrated a main effect of Distance-x ($F(4, 3.4)= 160.7$, $p< .001$), where all the distances were significantly different from one another, except distance 0 (M= 8, SE= 0.05) compared to distance 80 (M= 7.9, SE= 0.05), and distance 20 (M= 7.7, SE= 0.05) compared to distance 60 (M= 7.8, SE= 0.05), suggesting perfect symmetry between both sides of space (distance 40: M= 7.3, SE= 0.05). The main effect of Task was significant ($F(1, 3.4)=29$, $p< .001$), with execution time significantly slower at the MonAmour (M= 7.8, SE= 0.05) than at the control (M= 7.7, SE= 0.008) reaching tests. The Group by Distance-x interaction was also significant ($F(4, 3.4)= 2.8$, $p< .05$). For the healthy control participants, all the distances were significantly different from one another, except distance 20 compared to 60. Hemineglect patients demonstrated the same results, but in addition, distance 0 and 80 were not different from one another. For all distances, healthy control participants were significantly quicker than hemineglect patients. No significant interactions were found for Group by Task ($F(1, 3.4)= 1$, $p= .32$), Distance-x by Task ($F(4, 3.4)= 0.5$, $p= .70$), and the triple interaction Group by Distance-x by Task ($F(4, 3.4)= 0.2$, $p= .94$).

Peak speed analysis (Figure 2) showed a main effect of Group ($F(1, 3.4)= 12$, $p= .001$), with a quicker peak speed for healthy control participants (M= 38.6, SE= 1.6) than for hemineglect patients (M=25.7, SE= 3.4). The results also showed a main effect of Distance-x ($F(4, 3.4)= 63.2$, $p< .001$), where peak speed was significantly different for all distances, except between distance 0 (M= 36, SE= 1.9) and 80 (M= 35.2, SE= 1.9), and between distance 20 (M= 31.8, SE= 1.9) and 60 (M=30.7, SE= 1.9). This showed a perfect symmetry between left/contralesional and right/ipsilesional space, and an increasing peak speed towards the extremities of space compared to distance 40 (M=26.9, SE= 1.9). Results also showed a main effect of Task ($F(1, 3.4)= 94.7$, $p< .001$), where the peak speed at the control reaching test (M= 34.2, SE=1.9) was quicker than that at the MonAmour test (M= 30.1, SE= 1.9). A significant interaction for Group by Distance-x ($F(4, 3.4)= 5.2$, $p< .001$) demonstrated that for healthy control participants, all the distances were significantly different from one another except between distance 0 and 80, with an increasing peak speed from the centre (i.e., distance 40) to the extremities of space. For hemineglect patients, distance 40 was significantly slower than all other distances. Additionally, distance 0 was different from all the other distances except 80. For all distances, healthy control participants were significantly quicker than hemineglect patients. No significant interactions were shown for Group by Task ($F(1, 3.4)= 0.5$, $p= .48$), Distance-x by Task ($F(4, 3.4)= 0.2$, $p= .94$), and the triple interaction Group by Distance-x by Task ($F(4, 3.4)= 0.04$, $p= .99$).


(A1)
(A2)
HC
HN
Ln reaction time (ms)
9
8,5
8
7,5
7
6,5
0
20
40
60
80
Distance-x
(B1)
(B2)
Ln execution time (ms)
Distance-x
(C1)
(C2)
Peak speed (cm/s)
50
45
40
35
30
25
20
15
Distance-x

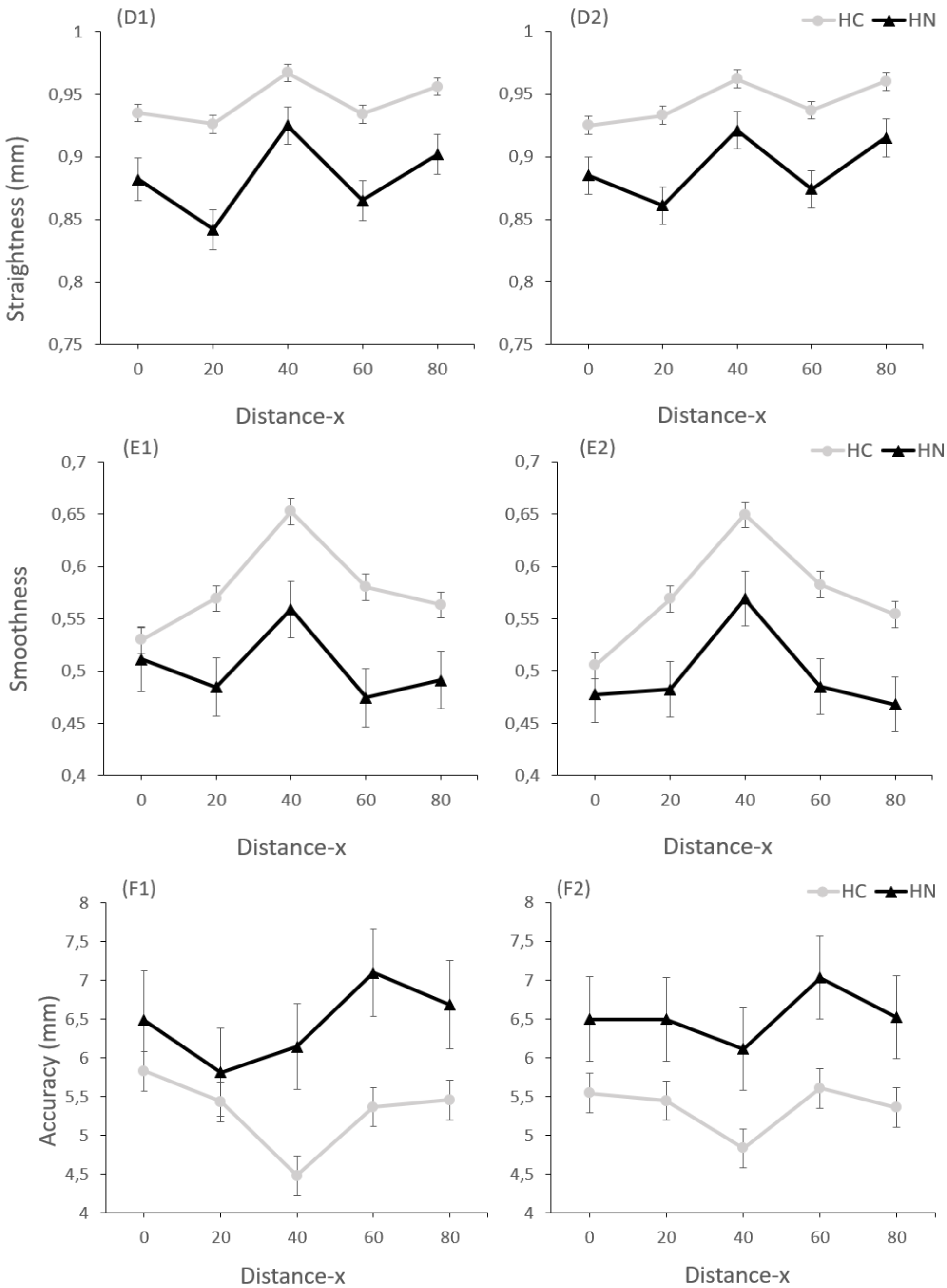


Figure 2. Action kinematics results for Experiment 1 (ipsilesional/dominant hand). In all figures, (1) corresponds to the MonAmour, and (2) corresponds to the control reaching tests for both groups. HC = Healthy control participants; HN = Hemineglect patients. The measures are: (A) Ln reaction time; (B) Ln execution time; (C) Peak speed; (D) Straightness; (E) Smoothness; and (F) Accuracy. Errors bars represent one Mean Standard Error.

Analysis of straightness (Figure 2) showed a main effect of Group ($F(1, 3.4)= 17.2$, $p= .002$), where hemineglect patients showed significantly less straight movements ($M= 0.87$, $SE=0.01$) than healthy control participants ($M= 0.94$, $SE= 0.06$). There was also a main effect of Distance-x ($F(4, 3.4)= 34.6$, $p< .001$), where all the distances were significantly different from one another, except between distance 60 ($M= 0.9$, $SE= 0.008$) and 0 ($M= 0.91$, $SE= 0.008$), 60 and 20 ($M= 0.89$, $SE= 0.008$), and between 40 ($M= 0.94$, $SE= 0.008$) and 80 ($M= 0.93$, $SE= 0.008$). There was no main effect of Task ($F(1, 3.4)= 1.36$, $p= 0.24$). There was a Group by Distance-x interaction ($F(4, 3.4)= 3.8$, $p= .004$), where healthy control participants demonstrated straighter movements to distances 40 (i.e., centre targets) and 80 in comparison to the other distances, with no significant difference between 40 and 80. For hemineglect patients, the results were similar, except that distance 80 was not different from distance 0, and that distance 0 and 20 were different from one another. For all distances, healthy control participants are significantly quicker than hemineglect patients. There were no significant interactions for Group by Task ($F(1, 3.4)= 1.4$, $p= .23$), Distance-x by Task ($F(4, 3.4)= 0.9$, $p= .43$), and Group by Distance-x by Task ($F(4, 3.4)= 0.1$, $p= .98$).

Smoothness analysis (Figure 2) showed a main effect of Group ($F(1, 3.4)= 9.9$, $p=.002$), whereby the movements of hemineglect patients ($M=0.5$, $SE= 0.02$) were significantly less smooth than for healthy control participants ($M=0.57$, $SE= 0.01$). Results also indicated a main effect of Distance-x ($F(4, 3.4)= 36.3$, $p<.001$), where movements to targets at distance 40 ($M=0.61$, $SE= 0.01$) were significantly more smooth than all the other distances (0: $M=0.5$, $SE=0.01$; 20: $M=0.53$, $SE=0.01$; 60: $M=0.53$, $SE=0.01$; 80: $M=0.52$, $SE=0.01$). There was no main effect of Task ($F(1, 3.4) = 1.4$, $p= .23$). The Group by Distance-x interaction was significant ($F(4, 3.4)= 4.4$, $p= .001$). For healthy control participants, movements were significantly smoother at distance 40 than all the other distances, and significantly less smooth at distance 0 and 80, except that distance 80 did not show difference with distance 20. For hemineglect patients, similar to healthy control participants, movements were significantly smoother at distance 40. Additionally, at distance 0, hemineglect patients were not significantly different from healthy control participants. There were no significant interactions for Group by Task ($F(1, 3.4)= 0.002$, $p= .97$), Distance-x by Task ($F(4, 3.4)= 1.1$, $p= .35$), and Group by Distance-x by Task ($F(4, 3.4)= 0.1$, $p= .95$).

Accuracy analysis (Figure 2) showed a significant main effect of Group ($F(1, 3.4)= 6.7$, $p= .01$) where healthy control participants were significantly more accurate ($M= 5.3$, $SE= 0.1$) than hemineglect patients ($M= 6.4$, $SE= 0.4$). Results also showed a main effect of Distance-x ($F(4, 3.4)= 4.9$, $p= .001$), where movements were significantly more precise to targets at distance 40 ($M= 5.3$, $SE= 0.3$) than at distances 0 ($M= 6.1$, $SE= 0.3$), 60 ($M=6.3$, $SE= 0.3$) and 80 ($M=6$, $SE= 0.3$). No significant results were found for the main effect of Task ($F(1, 3.4)= 0.2$, $p= .64$) and for the interactions Group by Distance-x ($F(4, 3.4)= 1.5$, $p= .19$), Group by Task ($F(1, 3.4)= 0.02$, $p= .88$); Distance-x by Task ($F(4, 3.4)= 0.4$, $p= .79$), and Group by Distance-x by Task ($F(4, 3.4)= 0.5$, $p= .73$).

3.3.2 Experiment 2

In this second experiment, only the reaction time was analysed as it was the only kinematic that demonstrated a lateralised bias towards the contralesional compared to ipsilesional hemispace in Experiment 1. As in the previous experiment, only correct responses on complete targets (i.e., trials where the participants reached the target within the virtual corridor in maximum 20000 ms) were included (healthy control participants: 99.8% for the non-dominant hand, 99.7% for the dominant hand; hemineglect patients without hemiplegia: 94.1% for the contralesional hand, 95.8% for the ipsilesional hand).

Ln reaction time analysis (Figure 3) demonstrated a main effect of Group ($F(1, 3.1)= 32.5$, $p< .001$), where the hemineglect patients were significantly slower ($M= 7.9$, $SE=0.08$) than heathy controls ($M= 7.4$, $SE= 0.03$). Results also showed a main effect of Distance-x ($F(4, 3.1)= 94.4$, $p< .001$) where all the distances were significantly different from one another (0: $M= 7.9$, $SE= 0.04$; 40: $M= 7.4$, $SE= 0.04$; 60: $M= 7.5$, $SE= 0.04$), except distance 20 ($M= 7.7$, $SE= 0.04$) compared to 80 ($M=7.7$, $SE= 0.04$). There was no significant main effect of Hand ($F(1, 3.1)= 0.03$, $p= .84$). The interaction Group by Distance-x was significant ($F(4, 3.1)= 25.5$, $p< .001$). For the healthy control participants, all distances were different from one another, except distances 0 compared to 80, and 20 to 60. For the hemineglect patients, all the distances were significantly different from one another, except distances 40 and 60. The Distance-x by Hand interaction was significant ($F(4, 3.1)= 2.9$, $p= .019$). For the ipsilesional/dominant hand, all distances were significantly different from one another. For the contralesional/non-dominant hand, all the comparisons were significantly different, except distance 20 compared to 80 and distance 40 to 60. There was no significant interaction for Group by Hand ($F(1, 3.1)= 0.9$, $p= .32$). Finally, the triple interaction Distance-x by Hand by Group showed significant results ($F(4, 3.1)= 3.9$, $p= .004$). For healthy control participants, for both hands, all distances were different from each other except distances 0 and 80, and 20 and 60. For hemineglect patients, for the ipsilesional hand, there were significant differences between all the distances, except between distance 40 and 60, and between 20 and 80. The contralesional hand of patients showed significant differences between all the distances except between distance 0 compared to 20, 40 compared to 60 and 80, and between 60 and 80.

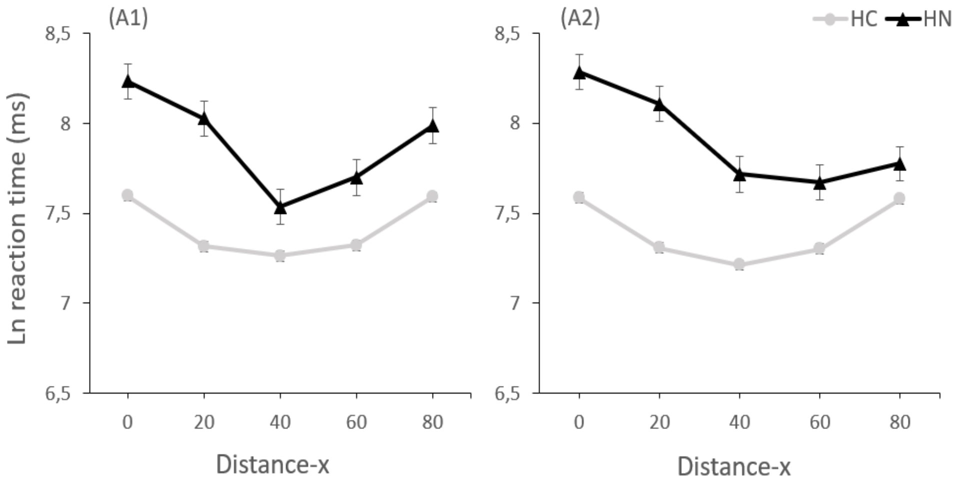


Figure 3. Action kinematics results for Experiment 2. (A) Ln reaction time for the MonAmour reaching test for both groups (1) the ipsilesional/ dominant, and (2) the contralesional/non-dominant hand. HC = Healthy control participants; HN = Hemineglect patients without hemiplegia. Errors bars represent one Mean Standard Error.

3.4 Discussion

In the literature, mixed findings are reported for visually guided action impairments in hemineglect (e.g., Heilman et al., 1985; Rossit, et al., 2009). The aim of this paper was to investigate reaching actions kinematics towards the contralesional versus ipsilesional hemispace in patients presenting left egocentric hemineglect compared to healthy control participants, manipulating attentional load and hand used. In Experiment 1, we hypothesized that action kinematics in hemineglect patients would demonstrate a lateralised bias towards contralesional relative to ipsilesional hemispace, and in comparison to healthy control participants. Additionally, we hypothesized that attentional load would cause greater lateralised impairments than no attentional load. Our results supported these hypotheses for reaction time, but not for the other action kinematic variables (i.e., execution time, peak speed, straightness, smoothness and accuracy). In Experiment 2, we tested a subset of hemineglect patients without hemiplegia and healthy control participants, and predicted that action kinematics would not differ between hand responses, with both hands showing a lateralised bias to contralesional compared to ipsilesional targets in hemineglect patients, and compared to healthy control participants. Our results supported this hypothesis. In the subsequent paragraphs, we discuss these results in relation to the literature.

Our results showed that for all action kinematics (i.e., reaction time, execution time, peak speed, straightness, smoothness and accuracy), hemineglect patients performed significantly worse than healthy control participants. This finding supports results reported in the literature showing a general reduced performance when comparing the actions of hemineglect patients to healthy control participants (e.g., Konczack & Karnath, 1998). This profile of performance reduction may be linked to the occurrence of a brain lesion rather than to a specific hemineglect deficit (see Ogourtsova, Archambault, & Lamontagne, 2015 for a review) . For example, research investigating movement kinematics of the ipsilesional hand after stroke, regardless of hemineglect, found that movements were slower, less smooth and had prolonged deceleration time compared to controls (Bustrén et al., 2017). This type of behaviour demonstrating a general abnormal slowness of the movement could be referred to as general bradykinesia (Konczack, Himmelbach, Perenin, & Karnath, 1999).

For the purpose of the current paper, we were particularly interested in the interaction between groups and distance-x. For these results, an absence of lateralised bias in hemineglect action execution kinematics was observed, namely for execution time, peak speed, straightness, smoothness and accuracy. Against our hypothesis, these results showed that patients with hemineglect reached equally well towards contralesional and ipsilesional targets. These results replicate previous studies measuring similar action execution kinematics such as execution time, peak speed, terminal accuracy and hand path (e.g., Karnath et al., 1997; Konczack & Karnath, 1998). However, our results differ from the studies of Mattingley, Bradshaw, and Phillips (1992, 1994) that showed actions kinematics impairments for movements towards the contralesional hemispace. This discrepancy in results may be explained by two possible factors. Firstly, hand-start position has previously been found to be critical for movement assessment in hemineglect (Duhamel & Brouchon, 1990). In the studies of Mattingley and colleagues, the starting position of the movement was not fixed and differed depending upon whether performing a leftward or rightward movement. In our tasks, the starting position was always aligned to the participant's body midline. It is therefore possible that impairments in action execution kinematics may be increased when the movements have to cross the body midline towards the contralesional space in contrast to movements that do not need to cross the midline (Corben, Mattingley, & Bradshaw, 2001). Secondly, the amount and the type of movement that was required in the present study was different to those required in previous studies. The studies of Mattingley and colleagues required several consecutive short movements on different targets in one single trial, whereas in our study, one single movement towards a unique target was required (Mattingley et al., 1992; Mattingley et al., 1994). As suggested by Corben et al. (2001), it is plausible that lateralised impairments are more pronounced in sequential movements, perhaps because spatial and temporal errors increase along the successive movements.

In support of our hypothesis, and contrary to the action execution kinematic results, the measure of reaction time in hemineglect patients demonstrated a lateralised bias, with an increased time for targets in contralesional compared to ipsilesional space (i.e., distances 0 and/or 20 compared to distances 60 and/or 80). This type of behaviour could be referred to as directional hypokinesia (i.e., abnormal slowness in movement initiation towards the contralesional hemispace; Heilman et al., 1985). However, in the context of this paper, we have to remain cautious in using this designation since the authors who defined this behaviour used a paradigm dissociating perception from action, which is not the case in the tasks used in the present study (Heilman et al., 1985). The contralesional slowness found in our results could be attributed to deficits either in target selection, or in the planning of action to the object, or a combination of these factors (Coulthard et al., 2006). This finding is supported by other studies. For example, Konczak, Himmelbach, Perenin, and Karnath (1999) reported that hemineglect patients had lateralised impairments in early planning of target-directed movement, but once the target was selected, the visuo-motor control of the movement was similar to the action kinematics of brain-damaged patients without hemineglect. This finding is consistent with the planning-control model (Glover, 2004). In this model, the “planning system” selects and initiates the most adapted motor program considering the environment and the actor’s objectives. More precisely, to achieve an action, the model considers: 1) the spatial characteristics of the target and actor, and the relation between them; 2) the non-spatial characteristics of the target (e.g., weight); 3) the main goals of the action; and 4) the visual conditions encircling the target. Based on this information, the planning system: 1) selects the target; 2) plans the movements for the spatial and non-spatial targets; 3) estimates the time of the movements; and 4) selects the action postural configurations. In contrast, the “control system” acts during the execution of action, and aims to reduce the spatial error of the movement using visual feedback, proprioception and prior instructions of the planning system (i.e., an on-line correction of the spatial parameters of the action). These two systems temporally overlap, the planning system being in charge of the initial definition of all the movement parameters and being highly effective at the beginning of the movement, and the control system being more and more influential as the movement unfolds (Glover, 2004). Therefore, in the present paper, the lateralised reaction time biases in hemineglect patients appear to be linked to a disruption of the “planning system” rather than the “control system”.

Although the above explanation is plausible for our results, it should be noted that other literature did not demonstrate a contralesional bias for reaction time (e.g., Rossit, et al., 2009). This could be explained by the extent of the damage and the severity of hemineglect at the time of the testing. For example, Mattingley et al. (1994) demonstrated slowness in contralesional initiation movements only in severe hemineglect. However, it is important to remain cautious with this explanation as it is highly difficult to compare patients’ severity of hemineglect across different studies with various diagnosis tools. Another reason explaining this discrepancy in reaction time results could be the complexity of the task (Rossit et al., 2009). It could be that responding to a single target from a maximum of three possible locations is much less complex than reacting to a target having thirty possible locations and being presented with distractors.

Concerning the attentional load manipulation, our results showed that reaction time, execution time and peak speed were quicker for the control reaching test without attentional load compared to the MonAmour reaching test with attentional load. The increased reaction time with the variation in attentional load (i.e., number of distractors) for both groups suggested that there was no pop-out effect in the MonAmour reaching test (Bricolo, Gianesini, Fanini, Bundesen, & Chelazzi, 2002), and rather that the MonAmour involves serial search. This is in line with the results shown by another study also investigating visual search in healthy participants and hemineglect patients (Fellrath, Blanche-Durbec, Schnider, Jacquemoud, & Ptak, 2012). Additionally, confirming our hypothesis, hemineglect patients showed greater contralesional compared to ipsilesional reaction time asymmetry for the MonAmour than for the control reaching test. More precisely, distance 0 and 20 were significantly different from 60 and 80 in the MonAmour, but only distance 0 was significantly different from 80 in the control test. This finding supports previous research where the presence of even one concomitant ipsilesional distractor makes the contralesional action planning more complex (Corben et al., 2001; Husain et al., 2000) and delays reaction time (Behrmann & Meegan, 1998). The effect of distractors can be explained by the ipsilesional distractors attracting and dominating selection (Corben et al., 2001; Fellrath et al., 2012). This is in line with the attentional model of Posner and Petersen (1990), which postulates a deficit in exogenous attention in hemineglect, especially in the disengagement of ipsilesional stimuli. Nevertheless, it was interesting to note that in our study, the control reaching test that was free from distractors still showed a contralesional bias. This suggests that even in a highly reduced attentional load test, the selection of the target and action planning was influenced by perceptual hemineglect.

In Experiment 2, the evaluation of the contralesional versus ipsilesional hand on the MonAmour reaching test showed similar results concerning lateralised bias. Both hand actions of hemineglect patients showed an asymmetry in the reaction time, where distances 0 and 20 were significantly slower than 60 and 80, whereas these distances were not different in the healthy control group. Supporting our hypothesis, these results imply that the lateralised bias in hemineglect seems independent of hand used. This finding adds to the earlier suggestion that hemineglect appears to influence the planning system (Glover, 2004) and not hand control factors. The results imply that higher-order planning before hand selection seems influenced by the hemineglect. These findings are interesting for the consideration of combined hemineglect and hemiparesis assessments and/or rehabilitation, where both deficits can be evaluated/rehabilitated with the contralesional hand within the same test/exercise. Such a project has been developed recently where the aim was to improve both hemineglect and hemiparesis impairments using a rehabilitation robot and an auto-adaptive serious game (Heins et al., 2017; Chapter 5).

Despite the small patient group, the analysis of results for Experiment 2 were consistent with our hypothesis. However, these results need to be confirmed with a larger sample of patients in future studies. Future studies using our tests should also include patients with motor upper limb weakness free from hemineglect to disentangle and confirm which action kinematic profiles are specific to hemineglect (e.g., is the contralesional reaction time bias only present in hemineglect patients? is the general bradykinesia of action execution kinematics present regardless of hemineglect? etc.). Additionally, attentional load effects could be better controlled if the tests are showed in a head mounted display, used for virtual reality task, avoiding potential influence of elements presented around the screen in the real environment.

In conclusion, Experiment 1 showed a general reduced performance in hemineglect patients compared to healthy control participants, but no lateralised asymmetry (e.g., contralesional versus ipsilesional hemispace) for ipsilesional hand action execution kinematics. However, the presence of a contralesional bias was demonstrated in reaction time. The manipulation of attention load showed a greater contralesional impairment in reaction time for the target search task with distractors (i.e., the MonAmour reaching test) than without distractors (i.e., the control reaching test). Experiment 2 showed no difference between hands for reaction time, with a lateralised effect towards the contralesional hemispace for hemineglect patients in comparison to healthy control participants. Our hypotheses were confirmed for the reaction time variable, but not for the other variables, suggesting that, for our patient sample, hemineglect seems to influence “planning” rather than “control” of the action. Further investigations including stroke patients without hemineglect will confirm which action kinematics are specific to hemineglect.

Chapter 4

Is visuo-spatial perception influenced by upper limb motor weakness?

Chapter 4

Is visuo-spatial perception influenced by upper limb motor weakness?

Abstract

Objective: The aim of the present study was to measure the influence of upper limb motor weakness on visuo-spatial perception in stroke patients. **Methods:** We tested fifty-five healthy control participants and nineteen hemiparetic first-stroke patients, twelve with and seven without hemineglect. Participants were asked to perform a target search task (the MonAmour test) on a robotic device, selecting the target presented among distractors as fast as possible. There were two versions of the task. In the pushing version, participants made a push response with the robot end-effector when they saw the target. In the reaching version, participants made a reaching movement to the target by moving the robot end-effector. Responses were made with the ipsilesional hand for patients and with the dominant hand for healthy control participants. Reaction times and omissions were measured for both tasks. **Results:** Healthy control participants showed slower reaction times to peripheral targets and a perfect symmetry between left and right space. All patients, irrespective of whether they had hemineglect or not, showed a longer reaction time for contralesional compared to ipsilesional targets. However, only patients with hemineglect demonstrated more omissions to contralesional than ipsilesional targets. For all groups, reaction times for the reaching task were slower than the pushing task. **Conclusions:** Compared to healthy control participants, a contralesional bias for reaction time exists in stroke patients regardless of the presence of hemineglect, suggesting a potential contribution of motor weakness to hemineglect symptoms. Results are discussed in terms of embodiment effects where action capability moderates perception.

4.1 Introduction

Research in embodiment theory suggests that perception is derived on the basis of the perceiver's capability to act with the body in the environment (Coello & Delevoye-Turrell, 2007; Witt, 2011). One common finding supporting this theory is that perception of space is encoded in terms of reachable peripersonal versus unreachable extrapersonal space (Bartolo, Coello, et al., 2014; Previc, 1998). Experiments that have manipulated action capabilities report an influence on perception. For example, when participants have to judge the slope of a hill while wearing a heavy compared to no backpack, under the same viewing conditions, participants wearing the backpack perceived the slope as steeper (Proffitt, 2006). This suggests that the effort required in action influenced perception. In the same vein, Bourgeois, Farnè, and Coello (2014) demonstrated that modifying arm length with the active use of a tool, thereby increasing action capability, caused increased perception of peripersonal space, making unreachable objects perceived as reachable. Grade, Pesenti, and Edwards (2015) asked participants to perform three perception tasks. In two tasks, they were presented with an object that was placed on a table at random locations along the mid-sagittal axis. In the first task, they were asked to judge whether they could reach to the object or not (i.e., reachability judgement task). In the second task, they had to estimate the distance of the object from themselves (i.e., distance estimation task). In a third task that was used as a control, two objects were presented with different lateral axis distances, and participants had to estimate the distance between the two objects. Critically, participants performed the tasks with and without a dual task of action ball squeezing, with the hypothesis that if perception is dependent upon action, the dual task should disrupt perception. The results supported the hypothesis for the two first tasks, showing increased response latencies, suggesting that egocentric perception of space appeared to be influenced by action. However, the allocentric perception of space (the third task), was not influenced by the dual-task action (see Iachini, Ruggiero, Ruotolo, Vinciguerra, et al., 2014 for similar results). These results suggest that action processes are involved in situations where the viewer has to evaluate space in relation to the body (i.e., egocentric perception), and not in situations where the body representation has less or no importance (i.e., allocentric perception).

Research on patients support the idea that action capabilities influence space perception. A recent study reported that, in a reachabilty judgement task, left-hemiplegic (right brain-damage) patients underestimated reachable space by 31% more than healthy control participants (Bartolo, Carlier, Hassaini, Martin, & Coello, 2014). This effect was demonstrated independently of whether the estimation was provided with the participants' healthy or hemiplegic arm. Further, an increased impairment was found for estimates in reference to the hemiplegic arm, suggesting that reduced action capabilities due to hemiplegia played a role in the perception of impairment was found for estimates in reference to the hemiplegic arm, suggesting that reduced action capabilities due to hemiplegia played a role in the perception of space. A similar study was conducted with hand amputee patients without brain-damage (Makin, Wilf, Schwartz, & Zohary, 2010). Authors used an adapted version of the landmark task, where two targets where presented either side of a fixation cross, and participants had to indicate which target (left or right) was further from the central fixation cross. Results showed that distances on the side of the amputation were underestimated. Participants considered both targets to be of equal distance to the fixation cross, when in fact the target on the side of the amputation was further away from the fixation cross than the other target. In the same vein, other researchers showed that prosthesis implantation to amputees restored peripersonal space perception (Canzoneri, Marzolla, Amoresano, Verni, & Serino, 2013). Another example comes from a recent study by Filbrich et al. (2017) who investigated visuo-spatial perception in patients with complex regional pain syndrome[1] and showed reduced action usage with their symptomatic limb. Authors used a temporal order judgement task where pairs of LED's were illuminated in near or far space, and patients were instructed to respond verbally to which LED they perceived as illuminating first (i.e., left or right). Their results showed slower responses for visual stimuli presented close to the symptomatic limb compared to those presented next to the unaffected limb, suggesting a reduced attention allocation in the portion of space where there was reduced action capability (however for alternative results, see Christophe et al., 2016; Förderreuther, Sailer & Straube, 2004).

Hemineglect disrupts visuo-spatial perception when reporting or responding to stimuli presented in the contralesional compared to ipsilesional hemispace, without a cause of elementary sensory or motor deficits (Heilman et al., 2000; Kerkhoff, 2001). Stroke patients exhibiting hemineglect often present with a concurrent motor weakness such as hemiparesis or hemiplegia (Kerkhoff, 2001; Ogourtsova, Archambault, et al., 2015; Sterzi et al., 1993). In clinical practice, the majority of hemineglect diagnosis assessments (e.g., line bisection tests, cancellation tests) involve manual responses made using the ipsilesional hand (Plummer et al., 2003) in order to circumvent the influence of the contralesional upper limb hemiparesis on measures of hemineglect. However, based on previous literature (e.g., Filbrich et al., 2017), it can be suggested that the influence of action impairment on perception could go beyond the actual use of the hand, meaning that even when responding with the ipsilesional hand or no hand, the presence of a motor impairment could still influence perception.

[1] A chronic pain condition characterised by sensory, motor, trophic and autonomic symptoms in one limb (Filbrich et al., 2017).

To our knowledge, no literature has clearly investigated the role of hemiparesis on visuo-spatial perception in patients with hemineglect. The only research close to this question demonstrated that active movements performed by hemineglect patients with their contralesional hemiparetic limb in the contralesional hemispace, improved visuo-spatial perception on conventional tests (i.e., limb activation therapy showing less contralesional omissions on the Star cancellation test) (O'Neill & McMillan, 2004; Wilson et al., 2000). Similar results have also been reported for hemineglect patients with robot supported movements (Choi et al., 2016; Varalta et al., 2014). These examples show that manipulations of hemiparetic limb action capability in contralesional space caused changes in hemineglect perceptual impairment, suggesting that hemiparesis may be partly involved in these perceptual deficits.

The aim of the present research was to measure the influence of action capability on visuo-spatial perception by comparing stroke patients with upper limb motor weakness (hemiparesis / hemiplegia), and with or without hemineglect, to healthy control participants. Comparison between the three participant groups should allow a better understanding of whether hemiparesis (/hemiplegia) contributes to the hemineglect condition. Participants' performance were compared using two versions of a target search task differing in the type of response, either pushing or reaching. Based on the embodiment literature, we hypothesized that both patient groups would demonstrate a perceptive contralesional bias relative to ipsilesional hemispace, and in comparison to healthy control participants. We also predicted that this contralesional bias would be greater in the hemineglect patient group than in the other patient group. Since the reaching response implicates a motor command in peripersonal space, we hypothesized that this type of response in comparison to the pushing response may further increase the perception deficits.

4.2 Methods

4.2.1 Participants

Patients were recruited using consecutive sampling from the neuropsychological, and physical medicine and rehabilitation departments of the Cliniques universitaires Saint-Luc and the Centre Hospitalier Neurologique William Lennox in Belgium. Patients were included if they had a history of first ischemic or haemorrhagic unilateral stroke, clinical diagnosis of motor upper limb weakness with or without clinical diagnosis of hemineglect (e.g., paper and pencil tests such as the Bells test), and comprehension of task instructions. The exclusion criteria were the presence of other neurological conditions such as dementia, or orthopaedic illness that limited upper limb function. Healthy adult participants paired by mean age were recruited. The Saint-Luc Biomedical Hospital-Faculty Ethics Committee approved the research protocol prior to any experimentation, and all participants volunteered to participate to the study providing a written informed consent. The study was registered at ClinicalTrials.gov (NCT02543424).

Nineteen brain-damaged patients (seven females) took part in this study (Table 1 & 2). Seven patients presented only motor upper limb impairment (i.e., hemiparesis or hemiplegia, named in this paper: hemiparesis group) and twelve presented both motor upper limb impairment and hemineglect (named in this paper: hemineglect + hemiparesis group). All patients in the hemiparesis group were never diagnosed with hemineglect (i.e., the group did not contain recovered hemineglect patients). The groups of patients did not differ in mean age (t(16.8)= 1.06, p= .30) and in months post-stroke (t(17)= 0.03, p= .97). All patients were right handed (as defined by the Edinburgh Handedness Inventory; Oldfield, 1971).

Fifty-five healthy control participants (thirty-seven females) aged between 50 and 79 years old participated in the study (Table 1). Seven controls were left handed (as defined by the Edinburgh Handedness Inventory; Oldfield, 1971). The mean age of healthy control participants was not significantly different from the hemineglect + hemiparesis group (t(13.2)= 0.78, p= .45) or the hemiparesis group (t(60)= 0.49, p= .62).

Table 1. Demographic characteristics of the three participant groups.

	Hemineglect + hemiparesis (n = 12)	**Hemiparesis (n = 7)**	**Healthy control participants (n = 55)**
Age (years), mean (SD)	65.5 (12.4)	61 (6.1)	62.6 (8.1)
Sex (male/female), n	7/5	5/2	18/37
Dominant arm (right/left), n	12/0	7/0	48/7
Lesion site (right/left), n	11/1	2/5	NA
Time post stroke (months), mean (SD)	11.8 (14.5)	11.6 (6.9)	NA
Upper limb weakness (hemiparesis/hemiplegia), n	5/7	5/2	NA

Note: NA= not applicable.

Table 2. Detailed demographic characteristics of the patients.

	N°	Gender	Age	Lesion	Months post-onset	Upper limb weakness
With hemineglect	1	F	51	Left haemorrhagic subarachnoid intracerebral stroke	8	HP
	2	M	68	Right haemorrhagic thalamic stroke	4	HP
	3	M	71	Right ischemic superficial middle cerebral artery stroke	35	HP
	4	M	72	Right ischemic middle cerebral artery stroke	48	HP
	5	M	84	Right ischemic middle cerebral artery stroke	5	HP
	6	F	47	Right haemorrhagic lentiform nucleus stroke	11	HPL
	7	F	52	Right ischemic middle cerebral artery stroke	6	HPL
	8	M	53	Right ischemic middle cerebral artery stroke	11	HPL
	9	M	62	Right haemorrhagic fronto-parietal stroke	5	HPL
	10	F	72	Right haemorrhagic intracerebral fronto-parietal stroke	2	HPL
	11	F	72	Right haemorrhagic intracerebral parietal stroke	3	HPL
	12	M	82	Right ischemic middle cerebral artery stroke	3	HPL
Without hemineglect	1	M	53	Left ischemic middle cerebral artery and internal capsule stroke	5	HP
	2	F	56	Right haemorrhagic central fissure stroke	12	HP
	3	M	58	Right haemorrhagic middle cerebral artery stroke	14	HP
	4	M	65	Left ischemic lacunar stroke	2	HP
	5	F	71	Left haemorrhagic thalamic and internal capsule stroke	22	HP
	6	M	60	Left haemorrhagic fronto-temporal and basal ganglia stroke	9	HPL
	7	M	64	Left haemorrhagic deep thalamic stroke	17	HPL

Note: M= male; F= female; HP= hemiparesis; HPL= hemiplegia.

4.2.2 Materials

4.2.2.1 Apparatus

The REAplan® (Axinesis) end-effector robot was used in this study (Figure 1). The robot is composed of an end-effector handle that is held in the participant's hand and allows for horizontal plane movements (93 x 52 cm). The robot comprises a screen placed in front of the participant (1920 x 1080 pixels) for the presentation of tasks, and a screen for the experimenter for exercise planning. Position and force sensors are integrated into the end-effector to measure the participant's actions. In the context of the present study, the robot was used in the active mode, meaning that it did not provide any assistance, but instead was used to measure the participant's active performance.

Figure 1. The REAplan® robotic device. The device incorporates: (1) an end-effector with position and force sensors, (2) a monitor for the participant and, (3) a monitor for the experimenter.

4.2.2.2 MonAmour tests

In the MonAmour target search task (Figure 2), participants were asked to find a target musical conductor randomly presented among distractor musical instruments (Montedoro et al., 2018; Chapter 2). Three different types of target were included in the test (Figure 3): a full musical conductor (with both arms; to measure egocentric hemineglect), and a half-left or half-right musical conductor (with one arm missing on the left or the right side; to measure allocentric hemineglect). The target and 119 distractors were placed within an invisible grid composed of 5 columns and 6 rows (30 cells), with 29 of the cells containing 4 distractor stimuli, and 1 cell containing 3 distractors and the target. The positions of these stimuli were randomised within each cell, but the target was always presented in the centre of the cell. During the test, each type of target was pseudo-randomly presented in one of the 30 cells so that each cell at some time contained each target over the course of the experiment (making 30 trials per type of target). Ten catch trials with no target were included in order to detect participants with impulsive behaviour, or participants who

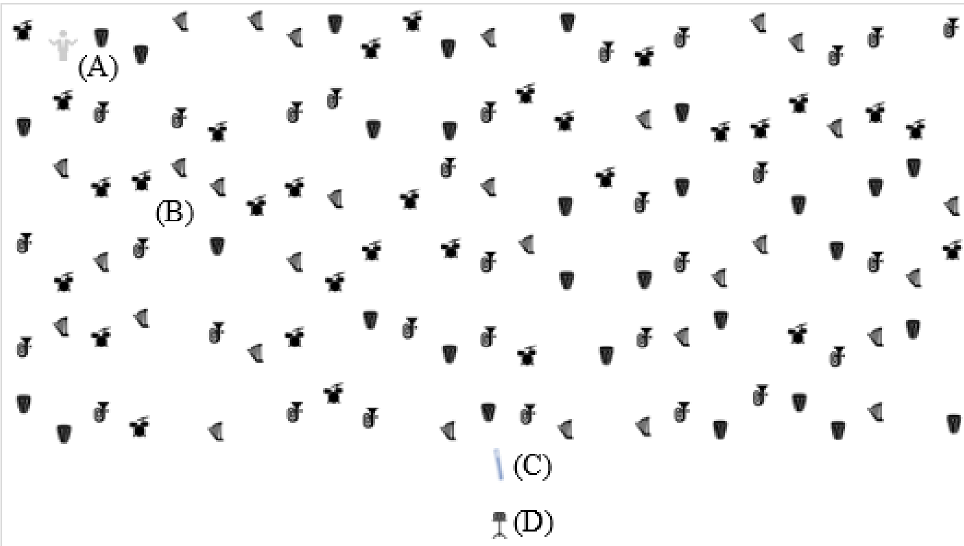


Figure 2. The MonAmour test. The test incorporated: (A) a musical conductor (target), (B) four different types of instruments (distractors), (C) the conductor's baton, and (D) the conductor's musical stand.

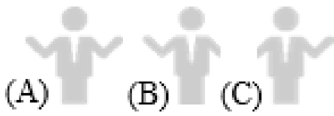


Figure 3. Illustration of the three types of targets (A) full target, (B) half-right target, and (C) half-left target.

misunderstood the instructions. The total 100 trials were presented in a random order, each separated by a fixation cross (1500 ms).

Two versions of task were used, one requiring a pushing response and the other one a reaching response, named the MonAmour pushing and MonAmour reaching respectively. In the MonAmour pushing, if the participants perceived a full conductor, they were instructed to push the end-effector of the robot towards the conductor's baton image (Figure 2). Alternatively, if they perceived a conductor missing one arm, they were instructed to pull the end-effector towards the conductor's musical stand image. In both cases, the handle was locked in a fixed position but could detect the force applied. Participants had a maximum of 7000 ms to make a response. If no response was made, the target was considered as omitted. The theoretical total pushing test duration ranged from 6 to 14 minutes (with an approximate duration of 9 minutes for a hemineglect patient omitting all the contralesional targets). In the MonAmour reaching, the participants responded by reaching to the position of full targets, and by reaching to the musical stand for the half targets. For all reaching responses, the baton indicated the position of the acting hand. At the beginning of each trial, the robot's end-effector was centred at the edge of the horizontal plane, aligned with the participant's body midline. Participants had maximum 7000 ms to initiate the movement towards the target or the musical stand, which had to be reached within a maximum of 20000 ms. If no response was made after 7000 ms, the target was considered as omitted. The theoretical total reaching test duration ranged from 10 to 33 minutes (with an approximate duration of 15 minutes for a hemineglect patient omitting all the contralesional targets). For both tasks, no response was required for catch trials.

To be assured that the participants understood the instructions, practice trials were performed before beginning the assessment. A break was made in the middle of the test, and participants were instructed that they could ask for additional breaks if needed.

4.2.3 Procedure

For all participants, the testing was conducted in two sessions (separated by to 2 to 5 days). One session involved the MonAmour pushing, and the other the MonAmour reaching. Session order was counterbalanced.

The position of the participants was standardised during testing. They were seated on a chair without wheels, and centred in front and at approximatively 52 cm from the participant monitor (visual angle of 84°). The horizontal plane height of the robot was adapted to the participant's height. Both versions of the test were performed with the dominant hand for healthy control participants and with the ipsilesional hand for patients. Eye and head movements were unrestricted to allow participants with potential visual field deficits to perceive the target across the contralesional and ipsilesional space. The tests were either administrated in a laboratory at the Faculty of Psychology at the Université catholique de Louvain, or in one of the two hospitals where the patients were recruited.

4.2.4 Data analyses

For the patients' data, left and right space was recoded to contralesional and ipsilesional space according to each patient's lesion side in order to standardise impaired space across the patients. The five invisible columns of the MonAmour tests were recoded using the term "Distance-x", from the extreme contralesional to the extreme ipsilesional space: 0 cm = extreme contralesional column, 20 cm = contralesional column, 40 cm = centre column, 60 cm = ipsilesional column, and 80 cm = extreme ipsilesional column.

Analyses were run using SPSS software (IBM, SPSS statistic 25) only on the full target trials (i.e., trials with the musical conductor with both arms). The dependent variables for both versions of the test were the omissions (%) and the reaction time of correct responses (ms). For the omissions analyses, no variance was found in the healthy and the hemiparesis groups (i.e., there was a floor effect, with very few omissions across Distance-x for both tasks; Figure 4). Therefore, the omissions were only analysed in the hemineglect + hemiparesis group by means of a generalized mixed model using a binary logistic regression with Task (i.e., MonAmour pushing response vs. MonAmour reaching response), Distance-x (0, 20, 40, 60, 80) and the double interaction as fixed effects, and Participants as a random factor. Reaction time data were transformed in natural logarithm (ln) to obtain a normal distribution. A generalized linear mixed model was used for the analysis of the reaction time. Group (healthy control participants vs. hemiparesis vs. hemineglect + hemiparesis), Distance-x, Task, and double and triple interactions were entered as fixed effects, and Participants was entered as a random factor. For post-hoc analysis, the sequential Bonferroni correction was automatically used in pairwise comparisons, both for reaction time and omissions ($p < .05$). For the pairwise comparisons of the significant main effects, the Mean (M) and Standard Error (SE) were reported.

4.3 Results

4.3.1 Omissions percentage

In contrast to the healthy and hemiparesis groups who showed almost no omissions (floor effect; Figure 4), the hemineglect + hemiparesis group showed omissions, with a main effect of Distance-x ($F(4, 700)=17.7$, $p< .001$; Figure 4). However, there was no significant result in the pairwise distance comparisons, no main effect of Task ($F(1, 700)=0.04$, $p=.84$) and no Task by Distance-x interaction ($F(4, 700)=1.3$, $p=.25$).

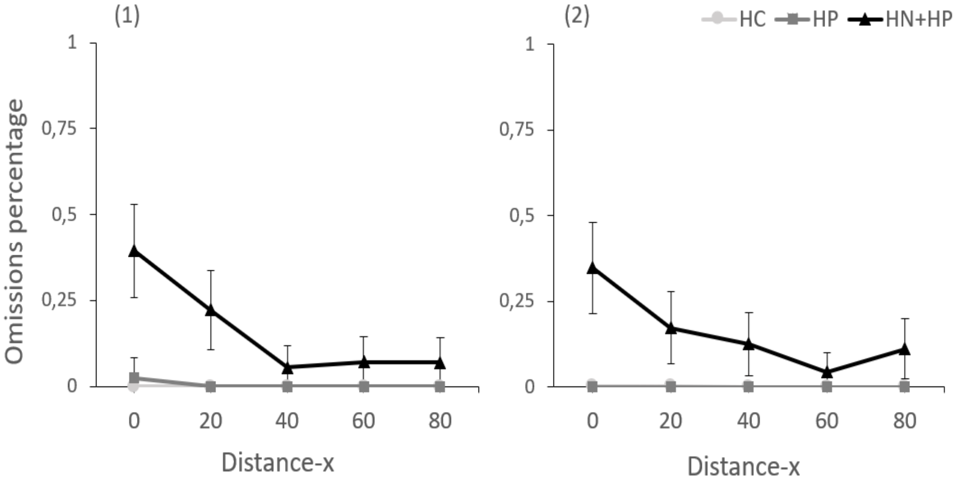


Figure 4. Percentage of omissions for the three groups across Distance-x on (1) the MonAmour pushing and (2) the MonAmour reaching. HC= Healthy control participants; HP= Hemiparesis group; HN+HP= Hemineglect + hemiparesis group. Error bars represent one Mean Standard Error.

4.3.2 Reaction time

Results showed a main effect of Group ($F(2, 4.5)=74.3$, $p <.001$; Figure 5). Post-hoc comparisons showed no difference in reaction time between the healthy control participants (M=7.3, SE=0.03) and hemiparesis patients groups (M=7.4, SE=0.08), but the reaction time of these two groups were both significantly quicker than the hemineglect + hemiparesis group (M=8.1, SE=0.06). The analysis also demonstrated a main effect of Distance-x (F(4, 4.5=213.8, $p<.001$; Figure 5). Post-hoc comparisons indicated that the reaction times were significantly different for all distances, with quicker reaction times for targets presented at distance 40 (M=7.4, SE=0.04), and prolonged reaction times for targets at distances 0 (M=7.9, SE=0.04) and 80 (M= 7.7, SE=0.04; distance 20: M=7.6, SE=0.04; distance 60: M=7.5, SE=0.04). Results showed a main effect of Task ($F(1, 4.5)=251.3$, $p <.001$; Figure

5). Reaction times for the MonAmour pushing (M=7.5, SE=0.03) were significantly quicker than for the MonAmour reaching (M=7.7, SE=0.03).

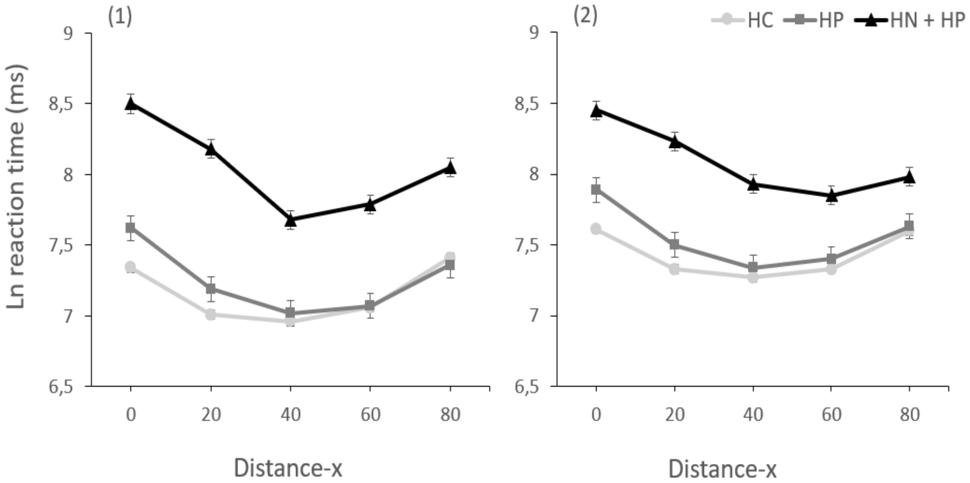


Figure 5. Ln reaction time (ms) for the three groups across Distance-x on (1) the MonAmour pushing and (2) the MonAmour reaching. HC= Healthy control participants; HP= Hemiparesis group; HN+HP= Hemineglect + hemiparesis group. Error bars represent one Mean Standard Error.

The Group by Distance-x interaction was significant (F(8, 4.5)= 37.3, p<.001; Figure 5). Post-hoc analysis indicated that for healthy control participants, the reaction times for all distances were significantly different from each other except for distance 0 compared to distance 80, and distance 20 compared to 60, showing a perfect symmetry between left and right space. Post-hoc comparisons for hemiparesis and hemineglect + hemiparesis groups demonstrated that reaction times for all distances were different from one another (including distance 0 compared to 80, and distance 20 compared to 60), with longer reaction times for contralesional targets, whereas there were no significant differences between distance 40 compared to 60. This demonstrates that the hemiparesis and hemineglect + hemiparesis groups showed asymmetry with slower reaction times in contralesional than ipsilesional hemispace. Additionally, post-hoc analysis revealed that for distance 0 and 20, the reaction times of the three groups were significantly different from each other. For the three other distances (40, 60, 80), the reaction times of healthy control participants were not significantly different from hemiparesis patients, whereas the hemineglect + hemiparesis group was significantly slower than the two other groups.

The Group by Task interaction was significant (F(2, 4.5)=41.2, p<.001; Figure 5). Post-hoc analysis showed that for the three groups, reaction times were significantly quicker in the MonAmour pushing than in the MonAmour reaching. The interaction was caused by a smaller, yet significant difference between tasks in the hemineglect

+ hemiparesis group. As in the main effect of group, for both tests, the reaction times of healthy control participants were not different from hemiparesis patients, but both were quicker than the hemineglect + hemiparesis group.

Finally, the Task by Distance-x interaction was significant ($F(4, 4.5)=4.5$, $p=.001$; Figure 5). Post-hoc analyses showed that, as in the main effect of task, responses to targets at all distances were quicker for the MonAmour pushing than the MonAmour reaching. Additionally, for the MonAmour pushing, the reaction times were different for all distances, whereas for the MonAmour reaching, the results were different for all distances except distance 20 compared to 80 and distance 40 compared to 60. The triple interaction Task by Group by Distance-x was not significant ($F(8, 4.5)=1.8$, $p=.07$; Figure 5).

4.4 Discussion

In the literature, it has been reported that action capability can shape and influence perception (e.g., Bartolo et al., 2014; Makin et al., 2010; Bourgeois et al., 2014). Interestingly, the deficit of hemineglect, that often disrupts visuo-spatial perception, frequently co-occurs with hemiparesis or hemiplegia (Kerkhoff, 2001; Ogourtsova, Archambault, et al., 2015). While it is common knowledge that hemineglect patients show a contralesional perception bias (Heilman et al., 2000), we might also expect, in line with the embodiment theory, a similar bias in patients with hemiparesis without hemineglect. This would suggest that the contralesional bias of some hemineglect patients might in part be explained by their hemiparesis. The aim of the present study was therefore to measure the influence of action capability on visuo-spatial perception, using two versions of a target search task differing in the type of response (i.e., pushing or reaching). We hypothesized that reduced motor capability would influence visuo-spatial perception, creating in patient groups with hemiparesis, a bias in perception for contralesional relative to ipsilesional hemispace, irrespective of hemineglect, and compared to healthy control participants. Moreover, we suggested that this contralesional impairment would be increased in patients with hemineglect (i.e., with the hemiparesis explaining part of the perception bias). Additionally, if this influence exists, we predicted that the effect would be greater in the reaching task than pushing task.

The healthy control and hemiparesis groups showed too few omissions to make statistical analyses (through a lack of variance). On the contrary, the hemineglect + hemiparesis group did show omissions, with the analysis revealing that the amount of omissions differed across space (i.e., Distance-x). Therefore, contrary to our hypothesis, these results did not demonstrate a visuo-spatial bias in the hemiparesis group (i.e., there was a floor effect).

The analysis of reaction time however was possible for all three groups. This analysis revealed that healthy control participants showed a perfect symmetry of responses between the left and right space, with a quicker reaction time in the centre space, and increasingly slower reaction times going towards the space extremities of target presentation. This finding replicates previous research also using a paradigm with increased eccentricity of targets (Smania, Bazoli, Piva, & Guidette, 1997). Interestingly, in the two patient groups, significant differences were found between the two hemispaces (i.e., distance 0 differed from 80 and distance 20 differed from 60), with slower reaction times for targets in contralesional and extreme contralesional hemispace relative to ipsilesional hemispace. Additionally, for the contralesional hemispace (i.e., distance 0 and 20), hemiparesis patients were significantly slower than healthy control participants, and hemineglect + hemiparesis patients were even slower than the hemiparesis group. For the other parts of space (i.e., distance 40, 60 and 80), the healthy and hemiparesis groups were not significantly different from each other, but significantly quicker than the hemineglect + hemiparesis group. The general slowness observed in the hemiparesis + hemineglect group compared to the other two groups could be accounted for by the combined negative effects of having two deficits, and by the non-lateralised impairment often accompanying hemineglect (Husain & Rorden, 2003).

Although hemiparesis patients managed to give their responses within the time limit (without omissions), in line with our hypothesis, their reaction time was slowed for targets presented in the contralesional compared to ipsilesional space, and compared to healthy control participants. The same effect, albeit stronger, was demonstrated in the hemineglect + hemiparesis group. These results could suggest that action capabilities have a potential influence on visuo-spatial perception as claimed by the embodiment theory (Proffitt, 2006; Witt, 2011), and illustrated by the clinical literature presented in the introduction of this paper (Bartolo, Carlier, et al., 2014; Filbrich et al., 2017; Makin et al., 2010). These findings suggest that egocentric visuo-spatial perception may require motor processes, where the position of the target is perceived in relation to the body, and to the action capability to interact with it (Grade et al., 2015). Based on these results, we could argue that hemiparesis appears to have a possible role in hemineglect symptoms. This link between perception and action impairments could have important implications for the understanding of hemineglect, both in research and in clinical practice. Consequently, future studies measuring hemineglect should be wary of the hemiparesis action impairment in the methods and the interpretation of results. Likewise, clinicians should consider this factor when evaluating the severity of symptoms and setting rehabilitation goals. These results provide evidence that the influence of hemiparesis on hemineglect goes beyond the choice of the hand used to perform the task. This means that even when performing a task with the unaffected ipsilesional hand, such as the MonAmour in this paper or in paper and pencil tests, the resulting performance could partly be altered by the motor capability.

Our hypothesis concerning the moderation of the type of response on the patients' perception impairments (i.e., reaching response increases contralesional bias compared to pushing response) could not be demonstrated due to an absence of significant triple interaction. Glover (2004) proposed a planning system responsible for target selection, movement planning, time movement estimates, and action postural configuration selection. In this sense, the perception impairments found in our results (i.e., slower reaction time for targets in contralesional compared to ipsilesional hemispace, with no differences between pushing and reaching responses) might be explained by a disruption to target selection rather than movement planning (that would perhaps show differential responses based on the type of movement planned). A clear finding concerning the comparison between the type of response was that all three groups took less time to respond to the MonAmour pushing task than to the MonAmour reaching task. Both tasks involved a similar perception component for the search and selection of the target, but the pushing versus reaching responses differed in complexity. This difference perhaps explains the additional time required through longer processes of action planning in the reaching version of the task (Coulthard et al., 2006; Glover, 2004).

Although our results appeared to support our hypotheses concerning an embodied effect for the perception of space in hemiparesis, another possible explanation may be considered. It is plausible that the accuracy of the MonAmour test (Montedoro et al., 2018; Chapter 2) allows a more precise measure of subtle visuo-spatial deficits compared to the tests currently used in daily clinical practice. This may mean that some patients categorized in the hemiparesis group using traditional tests may actually have a mild form of hemineglect that was previously not identified by the clinic, and these patients better correspond to the hemineglect + hemiparesis group. This interpretation raises an issue for other studies investigating the effect of action capabilities on perception. Even if the focus of these studies was not on hemineglect, and that authors excluded hemineglect patients from their sample, the tests used to define this categorization must be sensitive enough to detect the mildest forms of hemineglect. Future studies should therefore pay attention to adopt sensitive measures to define patient groups. Additionally, it could be useful to use brain imaging to have supplementary evidence that patients with hemiparesis do not have hemineglect. For example, Voxel-based Lesion-Symptom Mapping (VLSM) methods allow for correlation analyses between tissue damage (voxel-by-voxel) and behavioural responses (Bates et al., 2003). Some authors have used VLSM to distinguish the brain regions correlated with egocentric versus allocentric hemineglect (Chechlacz et al., 2010; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2009). In our case, the same method could be used to distinguish the brain areas correlated to hemineglect behaviour (e.g., from the MonAmour test) versus hemiparesis behaviour (e.g., from a dynamometer muscle strength measure). Using these methods, researchers could exclude patients with damage in regions responsible for hemineglect from a hemiparesis sample group.

In order to support the embodiment hypothesis suggested by the results of this paper, future studies should control the severity of the motor upper limb weakness since this factor influences the amount of actions performed with the contralesional upper limb, and in turn should influence the visuo-spatial perception by a predicted degree. Previous studies have demonstrated that an increase in physical effort induced a change in perception (Witt, Proffitt, & Epstein, 2004). In line with this result, if increasing motor weakness leads to an increasing contralesional bias, it would be an additional argument in favour of the embodiment hypothesis. Unfortunately, this analysis was not possible in our sample since the robot strength test that we developed for measuring motor upper limb weakness severity had not yet been validated (Dehem et al., 2018, manuscript submitted for publication). Additionally, we suggest that future studies should compare two groups of hemiparesis patients with right versus left hemispheric lesions matched by severity of motor upper limb weakness and by lesion size. If the results show that the influence of the motor deficit on visuo-spatial perception is independent of lesion side, the results would support the interpretation of an embodiment effect, similar to that shown by Makin et al. (2010). Alternatively, if the results show that the influence of the motor deficit on visuo-spatial perception is particularly influenced by a right side lesion, the results might support that the patients show a hemineglect deficit, which is more prevalent following right lesions (Ten Brink et al., 2017).

In conclusion, the present study measured the influence of action capabilities on visuo-spatial perception using two versions of a target search task (i.e., pushing or reaching response) in healthy control participants and stroke patients with motor upper limb weakness, and with or without hemineglect. Results in omissions demonstrated the presence of a typical contralesional bias in the hemineglect group but an absence of omissions in the two other groups. Results in reaction time showed a perfect symmetry in the speed of perceiving targets across space for healthy control participants, whereas slowness in perceiving targets on the contralesional hemispace was demonstrated in patients with motor impairment, irrespective of hemineglect. Our hypothesis was therefore confirmed for the reaction time measure, suggesting that these results could be interpreted in terms of embodiment, where reduced action capability causes a lateral bias in perception. This finding could lead to a better understanding of hemineglect symptoms when concomitant with hemiparesis. Contrary to our hypothesis, this lateralised bias was not emphasized in the reaching task in comparison to the pushing task. Further studies are needed to confirm these preliminary results and interpretations.

Chapter 5

Robotic-assisted serious game for motor and cognitive post-stroke rehabilitation

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Robotic-assisted serious game for motor and cognitive post-stroke rehabilitation

Abstract

Stroke is a major cause of long-term disability that can cause motor and cognitive impairments. New technologies such as robotic devices and serious games are increasingly being developed to improve post-stroke rehabilitation. The aim of the present project was to develop a ROBiGAME serious game to simultaneously improve motor and cognitive deficits (in particular hemiparesis and hemineglect). In this context, the difficulty level of the game was adapted to each patient's performance, and this individualized adaptation was addressed as the main challenge of the game development. The game was implemented on the REAplan end-effector rehabilitation robot, which was used in continuous interaction with the game. A preliminary feasibility study of a target pointing game was run in order to validate the game features and parameters. Results showed that the game was perceived as enjoyable, and that patients reported a desire to play the game again. Most of the targets included in the game design were realistic, and they were well perceived by the patients. Results also suggested that the cognitive help strategy could include one visual prompting cue, possibly combined with an auditory cue. It was observed that the motor assistance provided by the robot was well adapted for each patient's impairments, but the study results led to a suggestion that the triggering conditions should be reviewed. Patients and therapists reported the desire to receive more feedback on the patient's performance. Nevertheless, more patients and therapists are needed to play the game in order to give further and more comprehensive feedback that will allow for improvements of the serious game. Future steps also include the validation of the motivation assessment module that is currently under development.

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5.1 Introduction

Stroke affects fifteen million people each year worldwide, with approximately one-third of these patients having persistent neurological sequelae that causes deficits in motor functions and/or cognition (Mackay et al., 2004). Motor disorders can result in a loss of motor control, muscle paresis, proprioceptive deficits, spasticity and muscle shortening which decrease the upper limb range of motion (Pollock et al., 2013). Cognitive impairments after stroke can vary, but most frequently, impairments are to memory, executive function and attention (Jaillard et al., 2009). For the latter, the condition of hemineglect results in patients having problems to orient, perceive and respond to stimuli; either on the contralesional side of the space (egocentric hemineglect) or to the contralesional side of objects (allocentric hemineglect), or both in combination (Heilman et al., 2000; Rode & Pisella, 2011).

Interestingly, patients frequently have hemineglect with hemiparesis, which together, significantly hinders functional daily activities and prevents functional remission (Jehkonen et al., 2000; Pradat-Diehl et al., 2010). Although the brain typically undergoes spontaneous recovery after stroke (during the acute phase), one third of patients show persistent symptoms of hemineglect more than a year after the neurologic incident, and 25% of patients remain with upper limb motor impairments five years post-stroke (Geddes et al., 1996; Karnath et al., 2010). Therefore, there is a crucial need to develop news means of effective motor and cognitive rehabilitation.

Motor rehabilitation of upper limb impairment is usually based on motor learning principles. These principles strongly recommend: (i) intensive practice and associated movement feedback; (ii) task-specific training; (iii) motivating environments to enhance treatment adhesion; and (iv) use of assistance to facilitate or aid the patient’s responses (Kitago & Krakauer, 2013; Mehrholz et al., 2015). Hemineglect rehabilitation focusses on using (visual, auditory or tactile) cues to attract the patient to explore and attend the neglected contralesional side (R. S. Marshall, 2009).

The use of serious games in rehabilitation has considerably increased during the last years (Burke et al., 2009; Tomé, Pereira, & Oliveira, 2014a). The primary objective of serious games is not for entertainment, enjoyment or fun (Michael & Chen, 2005). In neurorehabilitation, the primary purpose of a serious game is for the improvement of motor and/or cognitive function. To this end, serious games allow for continuous adaptation of the exercise difficulty according to the patients’ abilities (Borghese, Pirovano, Lanzi, Wüest, & de Bruin, 2013). Indeed, the rate of success is a key factor of rehabilitation. If the exercise is too difficult, the patients will always fail, and they will not regain new skill. On the other hand, if the exercise is too easy, the patients will always succeed, without regaining any ability (Cameirão, Bermúdez i Badia, Duarte, & Verschure, 2011). According to Cameirão et al. (2011) and Perry et al. (2011), the success rate should remain between 50% and 70% to maximize the patient's improvements. In addition to facilitating learning, serious games can also be highly engaging and motivating, which facilitates involvement of the patient in the prolonged and intensive rehabilitation process (Burke et al., 2009). Research in the literature has already shown various potential benefits of serious games in stroke rehabilitation. For example, the single case study of Mainetti et al. (2013) demonstrated that the use of a video-game designed for hemineglect rehabilitation was positively accepted by the patient, and showed improved performance, both on standardised tests (e.g., line bisection), but also and in everyday life activities. Moreover, these improvements remained at the follow-up assessment five months after the rehabilitation session. In a second example, it was also shown that hemineglect patients included in an interactive virtual street crossing training improved their visuo-spatial performance, and in their ability to cross real streets (Katz et al., 2005). The patients paid more attention to the contralesional side of space, compared to hemineglect patients following a computer based visual scanning task. Similar results have also been reported for games tailored to rehabilitate motor deficits. A recent randomised control study of a rehabilitation gaming system used over twelve weeks showed that patients compared to controls presented significant improvements in the arm subpart of the Fugl Meyer Assessment Test, and the Chedoke Arm and Hand Activity Inventory (Cameirão et al., 2011). The patients also showed increased performance in their paretic arm velocity movement. Moreover, this study of Cameirão et al. (2011), and Burke et al. (2009) showed that motor rehabilitation games were highly accepted by patients.

Currently, post-stroke rehabilitation sessions in clinical routine or using a serious game are frequently specific to one type of disorder, either cognitive or motor. Consequently, patients have to undergo a lot of rehabilitation sessions in order to recover from both motor and cognitive impairments. However, it can be highly beneficial for the patient's rehabilitation to consider a combined approach to rehabilitate different impairments simultaneously (Cameirão, Faria, Paulino, Alves, & i Badia, 2016). Therefore, the aim of the present ROB*i*GAME project was the development of a serious game for combined motor (hemiparesis) and cognitive (hemineglect) rehabilitation following stroke, implemented on an end-effector rehabilitation robot, that complements existing clinical therapy. The advantage of the ROB*i*GAME rehabilitation robot and serious game is to provide additional rehabilitation possibilities to the patient, without the need of added therapists, thereby providing supplementary treatment support to the patient's current rehabilitation program. In this paper, after giving details on the chosen type of rehabilitation robots in Section 5.2, Section 5.3 describes the selected method for game development and difficulty adaptation based on individual real-time performance assessment. Section 5.4 focuses on the created serious game, features and parameters. Then, Section 5.5 presents the results of a first feasibility study that was conducted in order to validate the game characteristics. Finally, Section 5.6

gives details of a motivation assessment module which is currently under development and will be integrated to the game in future steps.

5.2 Upper-limb rehabilitation robots

Planar end-effector robots such as MIT-Manus (Krebs, Hogan, Aisen, & Volpe, 1998) and REAplan (Axinesis®; Figure 1; Gilliaux et al., 2014) are usually composed of (i) a handle movable on the horizontal plane, allowing movements of the shoulder and the elbow, (ii) force and position sensors, (iii) motors to assist or disturb the movement of the handle, (iv) a screen equipped with speakers and placed in front of the participant for the presentation of visual and auditory information, and (v) a monitor for the therapist to configure the exercise, and see the results of the patient's performance. These types of robotic devices are increasingly being used for upper-limb rehabilitation as they can fulfill the needs of intensive therapy, as well as provide a configurable amount of assistance, in coordination with combined haptic, visual and auditory feedback. For example, recent reviews showed an improvement of upper limb motor control and daily living activity after robotic assisted therapy (Mehrholz et al., 2015; Pollock et al., 2013). These robots also provide a quantitative assessment tool for measuring movement kinematics and kinetics (Gilliaux et al., 2014). These characteristics make such robots suitable for the development of post-stroke rehabilitation of both motor and cognitive impairments, and for the inclusion of serious game development.

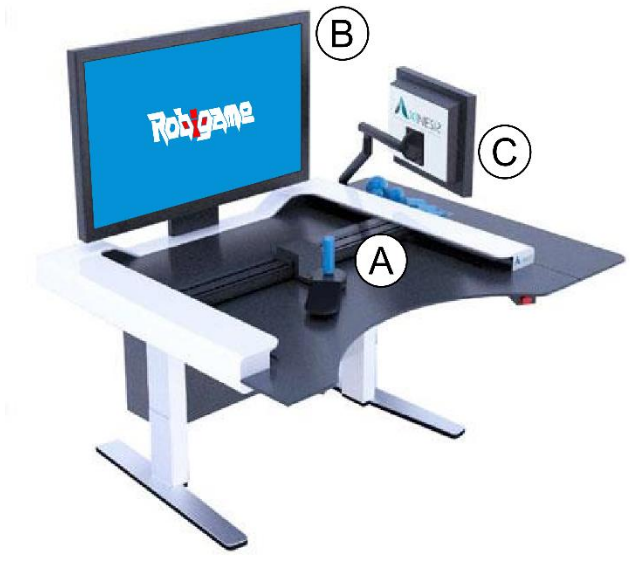


Figure 1. Illustration of the REAplan upper-limb robotic rehabilitation device (adapted from Axinesis SA (n.d)). The REAplan is composed of: (A) a handle equipped with position and force sensors that is actuated by two motors, (B) a screen and loudspeakers for the participant and (C) a monitor for the therapist.

During robot-assisted therapy for motor rehabilitation, the robot can provide motor assistance that consists in applying a given force on the end-effector to help the patient successfully complete the desired movement. Similarly, the participant’s movement can be disturbed by applying a resistive force on the end-effector to increase the task difficulty. If this resistive force is in the opposite direction of the movement, it allows training the participant’s force; if it is in another direction, it disturbs the participant’s movement and obligates him to adapt his trajectory.

In both cases, the computation of this force (direction and amplitude) can be configured so that the amount of provided assistance or resistance adapts to the patient’s performance continuously. More details on the force computation are given in section 5.4.

On the other hand, robot-assisted therapy for cognitive rehabilitation can combine (i) visual cues (e.g., highlighting a target on the screen), (ii) auditory cues (e.g., recorded spoken instructions), and particularly (iii) haptic cues (e.g., initializing the movement of the handle towards the target to be selected). Activation of lateralised cues help hemineglect patients re-orientate their attention to the contralesional space, the contralesional side of stimuli, or to activate the contralesional limb that may be underutilized. The type of provided help associated with trigger conditions (e.g., delays) can be configured and adapted to the patient’s cognitive performance.

The serious game presented in the following sections (ROB*i*GAME) is implemented on the REAplan but is meant to be adaptable to other similar devices.

5.3 Presentation of ROB*i*GAME

Developing a serious game for post-stroke rehabilitation to improve both motor and cognitive skills simultaneously highlights numerous challenges. One can name the task specifications and the regulation of the task difficulty, including the amount of motor assistance, in accordance to the patient’s performance which vary during a rehabilitation session, and from one rehabilitation session to another. Indeed, in order to optimize the patient’s rehabilitation, the game difficulty has to be continuously adapted to the motor and cognitive performance of the patient. The schematic representation of ROB*i*GAME (Figure 2) shows the proposed method for this regulation, independent of the type of task. In the proposed structure, the ROB*i*GAME can include several types of tasks such as target pointing, geometrical shape drawing, itinerary following, isometric force, etc. The planned tasks are single player tasks.

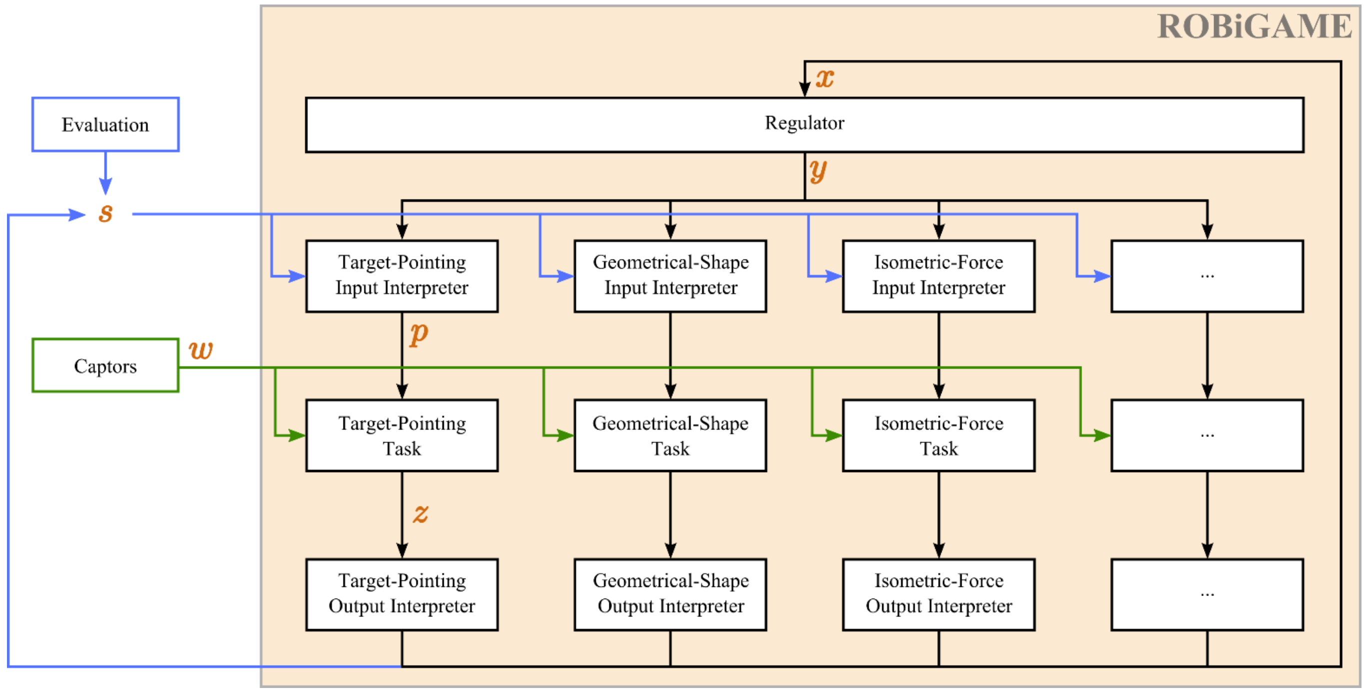


Figure 2. Schematic representation of the ROB*i*GAME regulation. The aim is to adapt the game difficulty to the patient's performance. The ROB*i*GAME can include several different types of task, with each one being associated with a set of task-specific parameters characterizing the task difficulty (***p***). The desired task difficulty is determined within a single regulator, which computes a set of difficulty indicators (***y***) that are common to all the types of task. An input interpreter translates these indicators into the task parameters, based on the patient's evaluation (***s***). Then, during the task performance, the game receives information from captors (***w***) and reacts in function of the captured data. When the task is completed, all the information that was measured during the task (***z***) is sent to the output interpreter, which translates it into performance indicators (***x***). The performance indicators are finally sent to the regulator, which computes the difficulty indicators of the next task.

In order to initialize the game difficulty, the patient's performance can be evaluated through the various motor and cognitive assessment protocols presented in Dehem et al. (2017) and Montedoro et al. (2017) respectively, before the first rehabilitation session. These results are stored (**s**) (Figure 2) so that they can be used to determine the difficulty level. The patient is also continuously assessed during the game, in order to update constantly the game difficulty to his evolution (e.g., improved performance or tiredness). The evaluation results include for example the patient's range of motion, as shown in Figure 3 in case of a left hemiparetic patient. In this figure, the dark blue area represents the "active" workspace that is reachable by the patient without assistance, whereas the light blue area is the "passive" workspace that he can reach with the help of a therapist. The game will never take the patient outside the passive workspace. The active workspace is expected to extend while the patient improves his motor skill, thus it will be updated continuously during the game.

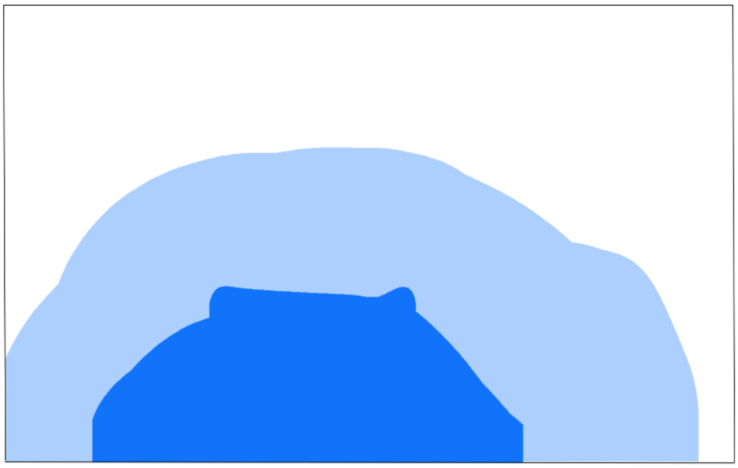


Figure 3. Illustration of the patient's range of motion obtained during the assessment protocol: typical trace of an actively reachable workspace (dark blue) and a passively reachable one (light blue) of a left hemiparetic patient.

Then, during the game, the desired difficulty is determined within a single regulator based on the patient's performance during the previous exercises and/or his assessment results. Indeed, the regulator computes a set of difficulty indicators (**y**) that are characterized in the exercise (e.g., an area indicator for the workspace or an assistance indicator for the amount of motor assistance). These indicators are common to all the types of task. However, each type of task is associated with a set of task-specific parameters (**p**) that characterizes its difficulty (e.g., the target position or the geometrical shape complexity). As a consequence, the difficulty indicators need to be translated into the task parameters within an input interpreter, which takes into account the results of the patient's evaluation (**s**).

During the exercise, real-time information is received from captors (e.g., the robot) such as position and force measurements (**w**) and the game reacts in function of the captured data (e.g., by increasing the amount of motor assistance or triggering cues). When the exercise is completed, all the information that was captured by the robot and the game (**z**) is sent to an output interpreter that transforms the information into performance indicators (**x**). These performance indicators characterize the motor and cognitive performance, and the motivation of the patient during the exercise he/she just realized (e.g., characterized by the amount of provided motor assistance, visual help or the patient's emotional state). Finally, these indicators are sent to the regulator, which then computes the difficulty indicators characterizing the next exercise.

In addition, during the exercise realization, images of the participant will be recorded and sent to a motivation extraction module that is currently under development. This module will analyse the patient's motivation through his attention and emotional state. Results will be used for two different purposes: (i) assessing to what extent the ROB*i*GAME achieves keeping the patient motivated, (ii) influencing the game scenario and difficulty level within the regulator. More details on this motivation extraction module are given in section 5.6.

Although the ROB*i*GAME structure allows the inclusion of several types of tasks, it was chosen to start the development with a target-pointing task, which is discussed in the next section.

5.4 The target pointing game

In the target-pointing game, a set of targets are displayed simultaneously on the screen. The participant has to reach some of them with the handle of the robot, and bring the target object to the starting point, one by one, and in a particular order. In order to select the theme for the scenery design of the game, a questionnaire survey evaluated the user preferences. Results showed that, in general, adults preferred games that were related to real life compared to fantasy games. Moreover, challenge and precise goals seemed to be the most two important features of the game preferred by the participants. Therefore, the theme selected for the scenery design was a sandwich store, where the participant was asked by the sandwich store manager to prepare sandwich orders for clients. However, the engine is generic enough to be adapted for other category of people (e.g., children) or scenarios, with the same game functionalities.

The target-pointing game was developed using the Unity Technologies, which is a popular 2D/3D multiplatform game engine of games and interactive experiences. It is object-oriented and provides a wide range of tutorials and excellent documentation. All the programming was made in C#.

5.4.1 Gameplay

When the game begins, the screen shows a client arriving at the sandwich shop and placing an order. The message of the client is personalised and mentions the name of the player. An example is shown in Figure 4. The list of ingredients that the participant has to find is displayed on a white board next to the client.

Once the participant is ready, the game continues on a second screen (Figure 5) that displays the following elements (see numbering in the figure): (A) the starting point, where the participant has to bring the targets after reaching them, (B) the workspace, where the targets are displayed, (C) the target to find, presented in the order of the recipe, and (D) the time remaining to find all the targets asked for the client. The position of (C) and (D) is bottom left by default, but both are placed on the bottom right of the screen in case of left hemineglect. The hand (E) follows the handle displacement. When the sandwich is finished, the game comes back to the first screen so that the completed order is given to the client. If the time runs out before the participant finds all of the targets, the exercise is indicated as unsuccessful and the client becomes angry and leaves without his order.

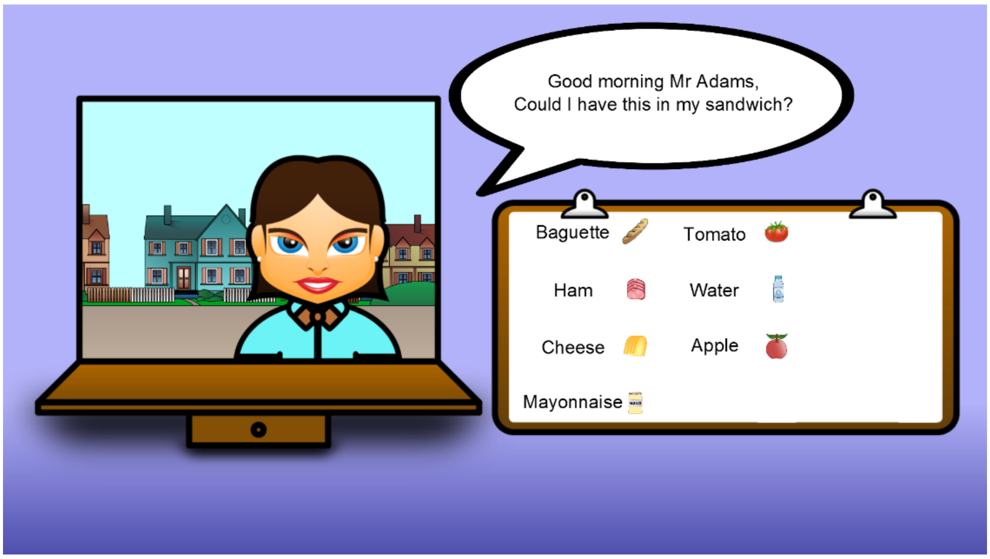


Figure 4. Illustration of a client ordering a sandwich in the sandwich store game. This screen allows the participant to have a first overview of the exercise (e.g., the number of ingredients of the recipe).

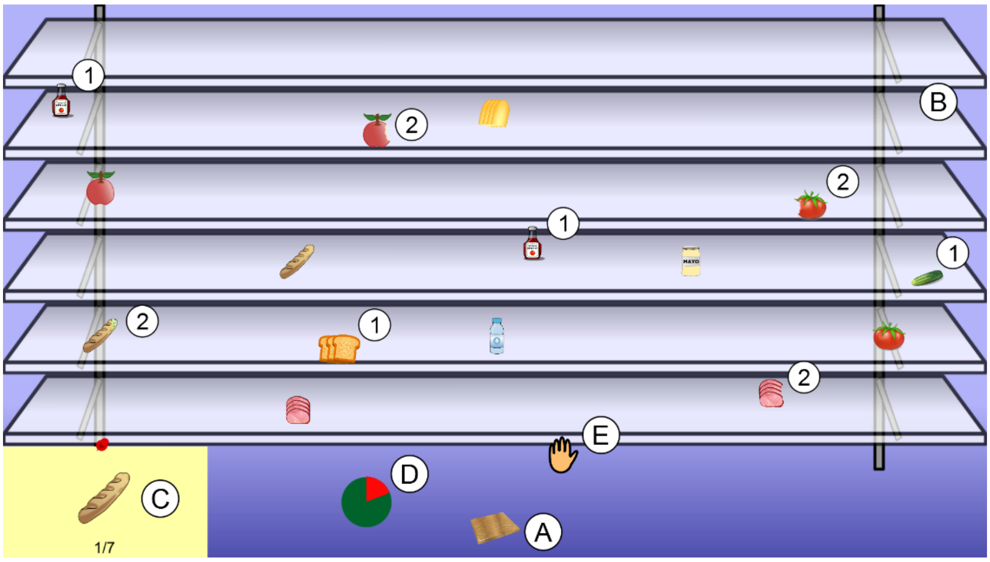


Figure 5. Illustration of the sandwich store counter. This screen shows: (A) the starting point, (B) the workspace, (C) the next target to catch, (D) the timer and (E) the cursor controlled by the handle displacement. In addition to the targets that the participant had to reach towards, the display also included (1) additional targets that were not part of the order, and (2) targets with a defect.

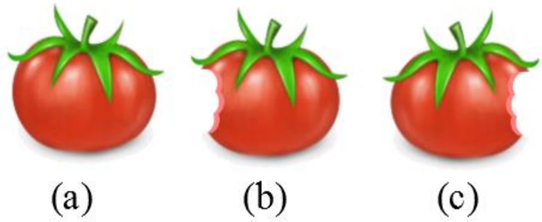


Figure 6. Illustration of a target (tomato) present in the sandwich store game: (a) target to reach, (b) target with a defect on the left side, (c) target with a defect on the right side. Targets (b) and (c) allowed for the assessment and rehabilitation of the left and right allocentric hemineglect respectively.

In order to influence the game complexity, two types of distracting elements can be displayed on the screen (see the corresponding numbering in Figure 5): (1) additional targets that were not asked by the client, and (2) targets with a defect (e.g., rotten or damaged) on one side (left or right). These elements should not be reached by the patient. A defect target corresponds to one of the targets that the player has to reach in order to compile the sandwich (see Figure 6 as an example). It is expected that patients with allocentric hemineglect might not see the defect on the contralesional side of the object, and would therefore not be able to make the difference between the real target and the defect one. Indeed, these defect targets were added to the task in order to encourage these patients to take into account the whole target in order to successfully complete the exercise.

During the game, cognitive cues can be triggered after a given period of time in order to help the patient to orient their attention towards the target. Three types of visual cues are used: targets with glowing edges, target enlargement and target rotation. Each cue has a different level of visibility in order to provide an incremental or more obvious help. Patients with weak hemineglect may require less cues, while patients with severe hemineglect may need high visibility cues or even motor help (see next paragraph) to facilitate their finding of the target object. The different levels of visibility of the cues can also allow to assess the improvement of the patient during the course of the rehabilitation programme.

Motor assistance during the game can be triggered to help the patient reach the target with the handle. The REAplan is a force controlled robotic device that allows the provision of assistive or resistive force during movement. The computation of this force is based on the definition of a reference trajectory (i.e., a trajectory that the participant should follow with the end-effector, based on the concept of virtual spring; see Figure 7). The assistance force combines two components: a lateral force (F_{lat}) and a longitudinal force (F_{long}). The lateral force is proportional to the distance between the end-effector actuated by the patient and the reference trajectory, and to a variable stiffness coefficient (k_{lat}). The longitudinal force is proportional to the difference between a reference speed (v_{ref}) and the speed of the end-effector actuated by the subject parallel to the reference trajectory, and to a damping coefficient (c_{long}). The stiffness and damping coefficients (i.e., k_{lat} and c_{long}) are positively or negatively incremented by a predefined value (Δk_{lat} and Δc_{long} respectively) at a given frequency *f*, based on a statistical analysis of the values of the position error and of the speed error respectively (Sapin & Galinski, 2016).

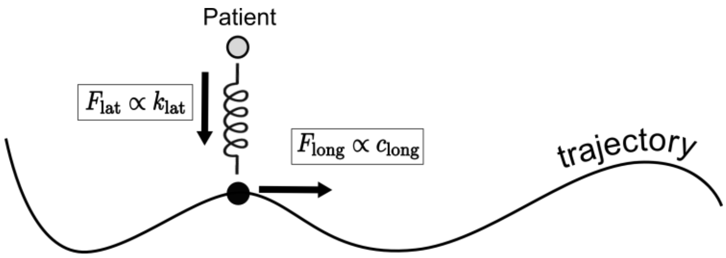


Figure 7. Operating method for the motor assistance. The force computation is based on the definition of a reference trajectory and combines two components: a lateral force (F_{lat}) proportional to a stiffness coefficient (k_{lat}), and a longitudinal force (F_{long}) proportional to a damping coefficient (c_{long}). The black point is the orthogonal projection of the patient's position on the reference trajectory (adapted from Galinski, 2014).

Several different types of feedback are provided during the game. Firstly, during the order preparation, a positive sound is activated when the player reaches to the correct target, and similarly a negative sound is activated when the player reaches to a distractor or a defect target. Also, when the target is dropped off at the starting point, glowing stars are displayed to show that the ingredient has been inserted in the sandwich. Secondly, at the end of each order, the ingredients that were reached correctly are highlighted in green on the white board, but the targets that were not reached are highlighted in red. Also, the mood of the client varies if the order is correct (happy) or if there are missing ingredients (angry). Finally, at the end of the session, the game informs the player about the number of successfully achieved orders from the total number of orders made by the client.

5.4.2 Game inputs

Each client's sandwich order can be configured to adapt the game difficulty to the patient's performance. In this way, it is possible to present more targets on the contralateral side in order to rehabilitate hemineglect, provide less motor assistance in order to rehabilitate hemiparesis, decrease the total time to perform the exercise, increase the number of distractors to make the task more challenging, etc.

The motor and cognitive difficulty of the target-pointing task is defined by setting the value of the following parameters:

- the number of targets shown on the screen, their position and the order in which they must be reached;
- the number of defect targets, the defected side (left or right), their position, and the position of the associated whole target;
- the number of distractors and their position;
- the total time taken to achieve the exercise.

Then, for each target to reach, it is also possible to define:

- the list of visual cues to display and their associated triggering period;
- the motor assistance parameters (the initiation values of k_{lat} and c_{long}, the values of v_{ref}, f, Δk_{lat}, Δc_{long} and the trigger period);
- the size of the selection zone: this parameter defines an area around the center of the target in which the participant has to select the target, independent of the image size. The size of the selection zone defines the required precision of the reaching;
- the validation time: this corresponds to the period of time the participant has to stay in the selection zone in order to select the target.

These parameters correspond to the set of parameters **p** (see Figure 2) and are adapted automatically for each exercise according to the patient's cognitive and motor performance.

5.4.3 Game outputs

The patient's motor and cognitive performance during each exercise are evaluated through the recording of a set of measured variables **z** (see Figure 2). These variables are:

- the total time needed for the exercise;
- the position of the handle over time;
- the force applied on the handle over time;
- the motor assistance parameters over time (k_{lat}, c_{long}).

Moreover, for each target that has to be reached, the following variables are obtained from the raw data:

- the movement initiation time, the time needed to reach the target and the time needed to bring the target object to the starting point;
- the triggering time of each visual cue and of the motor assistance;
- the list of distractors and defect targets that were reached, the time needed to reach the distractor/defect target, and the time spend on the distractor/defect target.

5.5 Feasibility study

In order to validate the usability, features and parameters of the target-pointing game, a feasibility study was run. The points of interest were: (i) the acceptance of the game by the patients, (ii) the enjoyment provided by the game, (iii) the graphic design, (iv) the visual cues and motor assistance, (v) information given to the patient during the game, and (vi) the effectiveness of the feedback. The second aim of the study was to determine more precisely the important features to take into account for the development of an auto-adaptive regulator.

Participants were recruited at the Cliniques universitaires Saint-Luc in Brussels. We selected two stroke patients (both with hemiparesis and one with hemineglect), and two therapists. The study was approved by the hospital ethics committee, and all participants gave their informed consent prior to participation.

For the purpose of the study, a scenario of ten client's orders varying in difficulty was proposed to the participants. If needed, the researcher manually modified the set of parameters **p** of each order to adapt the scenario better to the participant. Before the initiation of the scenario, the context of the game and the instructions were explained to the participant using an interactive training paradigm. After the ten client's orders, a questionnaire about the features of the game that used a 5-point Likert scale from "strongly disagree" to "strongly agree" was presented to the participant. A blank space was also provided to encourage the participant to report remarks. The duration of the session was approximatively 45 minutes per participant.

Results showed that the target pointing game had a lot of positive aspects, but also that some changes were essential. First, the patients enjoyed the game: both patients responded "strongly agree" to the playability of the game, and both indicated that they would like to play the game again. Patient A reported the desire to play the game alone, indicating that patients could be disposed to be rehabilitated by a game implemented on a robot without the presence of a therapist. Patient B particularly enjoyed the ecological aspect of the game, and noted that the clients were realistic (e.g., when showing an angry face because they didn't receive their order on time). As for the targets, therapists and patients strongly agreed that most of the target designs were realistic, except for the grated carrots and grilled aubergines that they indicated should be redesigned. Some target proportions should also be revised in order to be more consistent. The therapists suggested to increase the size of the targets in order to make them more easily perceived. However, both patients reported that the target size was adequate (indicating "strongly agree" on the questionnaire). A further study is required with more patients in order to be able to draw a firmer conclusion on the adequacy of the target size in the game, but we could consider adapting this parameter to the patient's performance, and to his visual acuity: greater targets for patients with a low performance level and smaller targets for patients with a high performance level. Therapists were sceptical that patients would be able to distinguish the defect target from the other targets. However, both patients succeeded to identify correctly the defect part of most targets. Patient B reported that the defect part of the slice of bread could be more pronounced, and therapist B found that the defect part of drinks was not sufficiently distinct to differentiate. In a future study, the defect targets design should be tested by patients with allocentric hemineglect. Patient B was not hemineglect, and yet he appreciated the inclusion of defect targets because it increased the diversity aspect of the game.

The visual cues aiming to help the patients find the target were not perceived during the game, except if the therapist showed the cue to the patients. Therefore, the cognitive help strategy should be reviewed. An idea could be to present only one visual cue to the patients, and if they still do not perceive the target, an oral cue could be given to encourage the patients to examine all of the workspace. Patient B reported that the target enlargement was the most visible cue. However, these observations should be confirmed in a future study by including more patients. For motor assistance, once triggered, the amount of assistance seemed to be well adapted to the patient's performance. However, the triggering conditions of this assistance should be reviewed. Currently, the motor assistance starts after the appearance of the visual cues. Consequently, patients need to wait a few seconds before receiving assistance to reach the target, although they had already perceived it. This aspect could frustrate the patient. Therefore, the triggering conditions of the assistance must be changed to detect when the patient perceives the target.

During the study, we noticed that patients seemed to receive too much information at the beginning of the game. This shows that the training of the game was essential to explain all the gaming features (e.g., the timer showing the remaining time to make the sandwich or the paper showing the target to catch and its order in the recipe). Note that, patients did not pay attention to the timer during the game, and this could be due to the design or position of the timer. One solution could be to increase the size of the timer and move it to the top of the screen. A sound could also ring out during the last seconds.

Finally, regarding the feedback, patients and therapists reported that the auditory feedback was appropriate. Patient B was willing to receive more feedback on his performance, in particular on the time he took to complete the sandwiches, as he was asked to do the exercise as fast as possible. Therapist B noted that the amount of feedback should be increased when failing a sandwich. He suggested that the game could show the patient which targets he failed to reach and its location. He also suggested to display the already reached targets near the counter during the exercise. Finally, patients and therapists appreciated the client change of mood when he didn't receive his order.

5.6 Development of a motivation assessment module

Recovering from post-stroke cognitive and motor impairments requires a prolonged and intensive rehabilitation, which can discourage the patient. Therefore, ensuring that the patient remains involved and motivated is a goal pursued by the ROB*i*GAME project. Towards this goal, it seems interesting to assess the patient's motivation during the serious game. The objective of this measure is twofold: firstly, it would allow to assess to what extend ROB*i*GAME achieves the goal of keeping the patient motivated during the game, and confirm that the developed game is appropriate for stroke patients; secondly, the extracted motivation could be used during the game regulation to influence the difficulty level, together with the motor and cognitive information that has been already captured.

A motivation extraction module is therefore under development for integration into a future version of the ROB*i*GAME. This module requires the use of a 3D camera: the Kinect V2 sensor with Microsoft Kinect SDK (Rocca, De Deken, Grisard, Mancas, & Gosselin, 2015). The compatibility of this material with the REAplan robot and the conditions of use (e.g., the luminosity) has been previously pre-tested. The camera will be positioned on the top of the screen, in front of the participant. The captured patient's behavior will be used to extract two features: (i) the patient's gaze (based on the head direction) and (ii) his emotional state (Rocca, Mancas, & Gosselin, 2014). The patient's gaze reflects his attention during the game. If the patient pays attention, his gaze will focus on the screen. Given the technical limitations of the camera position (i.e., the distance from the participant), it is not possible to access the participant's eyes orientation. However, according to Murphy-Chutorian and Trivedi (2009), we can consider that the gaze direction is closely matched to the head direction, as validated by Rocca et al. (2015), and Abe and Makikawa (2009) in healthy participants. This hypothesis will however be verified during a clinical trial with stroke patients in future stages of the project. Therefore, in the current project, head direction will be obtained from the Kinect user skeleton tracking and used to determine the patient's attention. Furthermore, for emotional state, it is possible to extract expressive parameters from the patient's face, such as "FACS" which are basic units related to the facial expressions (Ekman & Friesen, 1978). These parameters will be used to determine positive, neutral or negative expressions (e.g., pronounced involvement or fatigue). The proposed method has been validated with healthy patients, as shown in Figure 8 for the detection of a happy face. Again, the proposed method will be validated during a clinical trial with stroke patients.

5.7 Conclusion and perspectives

In this study, we implemented a target-pointing game on an end-effector robotic device, the REAplan. Our goal is to create a robot assisted serious game to rehabilitate both cognitive and motor impairments following stroke. The structure of the game allows to assess the patient's performance, and to adapt the game level accordingly, during the rehabilitation session and from one session to another. A set of input parameters of the game were identified and tested during a feasibility study.

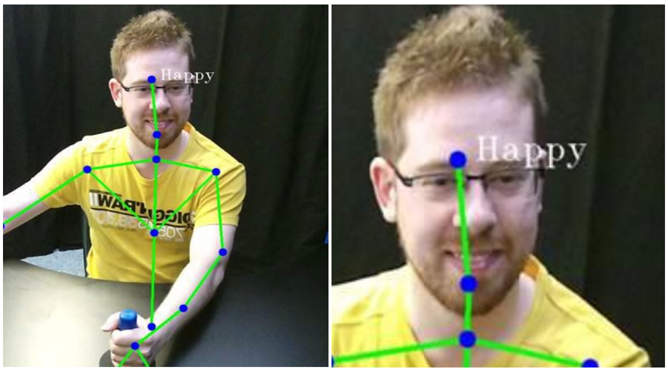


Figure 8. Illustration of body tracking with a happy face detection.

This study showed that patients and therapists enjoyed the game, and that patients would like to play the game again. The game was reported to be entertaining because of the large number of targets, the variety of challenge and distracting elements. However, the cognitive help strategy, and the triggering conditions of the motor assistance need to be reviewed. The game should also give more feedback on the patient performance during the game. Future steps include testing the sandwich store game with more therapists and patients, in particular with allocentric hemineglect disorder. Indeed, more data should be collected to highlight other possible issues of the proposed game and modify the required characteristics. Then, the new version of the game should be tested in a clinical trial with stroke patients. Finally, the motivation assessment module extracts the patient's gaze and emotional state to evaluate the patient attention and motivation during the game. This module is currently under development, and will be integrated into the serious game.

Chapter 6

Methods to objectively auto-adapt serious game difficulty for hemineglect rehabilitation

Chapter 6

Methods to objectively auto-adapt serious game difficulty for hemineglect rehabilitation

Abstract

Objective: The objective of the present paper was to investigate methods to auto-adapt rehabilitation serious game difficulty in correspondence to a hemineglect patient's individual performance and impairment severity, manipulating attentional load (Experiment 1), and cue types (Experiment 2). **Methods:** Both experiments used a sandwich shop serious game ran on a robot device. Participants were asked to search for the target (a sandwich ingredient) and reach to it as quick as possible. Experiment 1 tested the influence of attentional load on target detection. In this experiment, testing 20 healthy participants, the sandwich ingredient was presented with 0, 48, 96 or 144 distractors. Experiment 2 tested the influence of cue types on target detection. In this experiment, testing 11 hemineglect patients, the target was presented with 144 distractors and a cue chosen from 8 different possible cues (e.g., visual, auditory, haptic), or a no cue control condition. For both experiments, reaction time was recorded. **Results:** Reaction time for target detection increased linearly with the number of distractors in Experiment 1, providing an equation for determining game difficulty in function of attentional load. Experiment 2 showed that all cues significantly helped patients detect the target on the contralesional side of space (showing a quicker reaction time) relative to the control condition. Additionally, the cues could be divided into two groups respective to their level of help. **Conclusions:** The two experiments allow for an objective regulation of game difficulty using a linear equation for attentional load or using cues of different efficacy. This auto-adaptive serious game provides new possibilities for hemineglect rehabilitation.

6.1 Introduction

Hemineglect is characterized by an inability to attend to stimuli presented in space contralateral to the brain lesion (Heilman et al., 2000). The impairment significantly influences daily activities, especially personal grooming, eating and displacement (Pradat-Diehl & Peskine, 2006; Pradat-Diehl et al., 2010). Patients for example have difficulties to eat the food placed on the contralesional side of the plate, or to walk without bumping into a wall (Nijboer, Van de Port, Schepers, Post, & Visser-Meily, 2013). Despite spontaneous brain recovery and the use of conventional therapies, hemineglect persists in one third of patients more than one year after the neurologic incident (Farne et al., 2004; Jehkonen, Laihosalo, Koivisto, Dastidar, & Ahonen, 2007; Karnath et al., 2010; Kerkhoff & Schenk, 2012). Therefore, there remains an essential need to develop new methods to improve the recovery of patients.

In recent years, there has been increased interest in the use of serious games for improving the efficacy of clinical treatment (Burke et al., 2009; Tomé et al., 2014a). Serious games are defined as games where the primary purpose is not entertainment, but rather to teach or facilitate the development of skills (Rego, Moreira, & Reis, 2010). The games provide safe real-world scenarios that are highly motivating, capture attention, encourage motor coordination and spatial orientation, and facilitate patient involvement in prolonged and intensive rehabilitation (Tomé et al., 2014a). The focus is to improve impairments to achieve greater autonomy. Although commercialised games could also be used for rehabilitation, there remains a lack of appropriate games that meet the needs of brain-damaged patients (Mainetti et al., 2013; Tomé et al., 2014a).

In the emerging development of serious gaming for neurological deficits, some games rely on a static adaptation of game difficulty decided by the therapist. This can lead to failures caused by an under- or over-estimation of the patient's performance. For example, the patient may be bored, causing the therapist to assume an underestimation of patient capability. This error in judgment would lead to the game being too easy (not challenging) for the patient, which has been shown to decrease motivation and withdrawal from the game (/treatment) (Burke et al., 2009). However, an important and innovative feature of a serious game is that it can be dynamically tailored to the patient's individual ability through the constant evaluation of performance, leading to an objective setting of game difficulty (Gouaïch et al., 2012). For example, in the study of Cameirão, Badia, Oller, and Verschure (2010), the level of difficulty was adapted depending on the patient's motor performance (speed, range, interval, size) when reaching spheroids during a calibration task. The level of difficulty was increased by 10% if the patient reached at least 70% of the spheres or decreased by 5% if the patient reached less than 50% of the spheres. In the same vein, Gouaïch et al. (2012) developed an auto-adapted difficulty game using a virtual ant algorithm in order to define an "ability zone" representing areas of 2D workspace that the patient was able to reach with ease versus less able to reach. Areas that were reached several times were considered as easy, and less reached areas, as difficult. After consecutive successes, difficulty was increased by selecting areas just outside the ability zone, whereas after several failures, difficulty was decreased by selecting areas inside the ability zone. If the patient reached a steady state level, the same difficulty level was maintained. Another example of an auto-adapted serious game was presented by Grimm, Naros, and Gharabaghi (2016). They developed a virtual reach-to-grasp training using closed loop difficulty where the patient had to grasp a ball, carry it to a distant basket, and release it. Whenever the task was succeeded twice, an auto-adaptive algorithm enlarged the distance between the ball and the basket. However, if the task was failed, the distance was reduced. Similarly, the grip force required for reaching and releasing the virtual ball was increased whenever the threshold was achieved three times in a row and decreased if the patient had a difficulty to apply the force needed when interacting with the virtual ball.

Studies have demonstrated good acceptance of serious games by patients in the treatment of cognitive deficits, and increased motivation and engagement in therapy (Mainetti et al., 2013). Cognitive serious games have been developed for memory, speech, decision making, visuo-spatial perception and attention (Bartolomé, Zorrilla, & Zapirain, 2010; Cagatay, Ege, Tokdemir, & Cagiltay, 2012; Caglio et al., 2009; Hussaan, Sehaba, & Mille, 2011; Torrente, Del Blanco, Moreno-Ger, & Fernández-Manjón, 2012). For visuo-spatial perception and attention, Mainetti et al. (2013) reported a single case for hemineglect rehabilitation using a reaching task serious game. In the game, the patient had to move their hand to hit targets avoiding potential distractors (e.g., hitting white but not yellow seashells on a beach). Results showed an improvement in the patient’s performance on standardised clinical hemineglect tests (e.g., line bisection test), even after 5 months follow-up. The patient also improved on global cognitive functions (e.g., Attentional Matrices) and everyday life activities (e.g., reading newspaper). Another group of researchers tested a similar serious game on 24 hemineglect patients divided into experimental and control groups (Y. M. Kim et al., 2011). Patients in the experimental group used their non-paretic arm to touch flying birds, to catch coconuts falling from a tree, and to move boxes from one part of space to another. Compared to the control group, the experimental group demonstrated increased performance after treatment on the Star Cancellation test and the Catherine Bergego scale. Similar results were also found in a study using a street crossing serious game where patients had to cross the street avoiding vehicles coming from left and right space (Katz et al., 2005).

Despite these encouraging serious game examples, little development has been made on methods to objectively moderate game difficulty for hemineglect rehabilitation. For example, making the game easier with the use of cues to reorient attention, or the implication of distractors to increase visual attentional load and game difficulty. Some papers have reported the use of different cues and different levels of difficulty.

For example, in Mainetti et al. (2013), game difficulty was modulated by adding more objects to the scene (see also Katz et al., 2005), and by presenting a visual (i.e., blinking target) or an auditory cue (i.e., 3D sound from two speakers depending upon target position). However, these studies did not explain how they chose the methods to moderate game difficulty (e.g., why adding 9 distractors instead of 5 to increase task difficulty, or why using the visual / auditory cue, and whether or not these cues objectively reoriented attention?).

The global aim of the present paper was to investigate methods to objectively auto-adapt serious game difficulty in correspondence to a patient's individual performance for hemineglect rehabilitation. The methods manipulated attentional load and cue types. Experiment 1 tested healthy participants and measured how attentional load influenced game difficulty by measuring the influence of increasing numbers of distractors (i.e., 0, 48, 96 and 144) on target detection reaction time. We hypothesized that increased attentional load would linearly increase game difficulty. Experiment 2 tested hemineglect patients and investigated how cues influence game difficulty by measuring the influence of different cue types (i.e., 8 different cues, either visual, auditory or haptic) on target detection reaction time in the contralesional hemispace. We hypothesized that cues would make the game easier, allowing patients to detect targets quicker in the contralesional hemispace relative to a no cue condition. Moreover, we hypothesized that efficacy in target detection would be moderated by cue types.

6.2 Experiment 1: Influence of attentional load on game difficulty

6.2.1 Methods

6.2.1.1 Participants

We recruited twenty healthy participants (twelve females) without neurological history, perceptive or motor deficits. Participants were aged between 49 and 78 years old (mean (SD) = 61.4 (8.8)) and two were left handed. All participants volunteered to participate and provided written informed consent in accordance with Saint-Luc Biomedical Hospital-Faculty Ethics Committee who approved the research protocol prior to any experimentation. The study was registered at ClinicalTrials.gov (NCT02543424).

6.2.1.2 Materials

6.2.1.2.1 Apparatus

The experiment was run on the REAplan® robot (Axinesis; Figure 1). This device is an end-effector robot that allows for movements of the upper limb in the horizontal plane (93 x 52 cm). The robot is composed of a screen for the participant (1920 x 1080 pixels) and a screen for the therapist. It provides precise measurements through position and force captors (125 Hz) located in the handle of the device. The robot has three modes of functioning: (1) active mode where the participant performs the movement alone (i.e., no assistance provided by the robot); (2) the passive mode where the robot guides the movement of the upper limb; and (3) the active-passive mode where the robot helps the participant's upper limb movement as needed. In the present paper, the robot was used in the active mode to record participant performance.

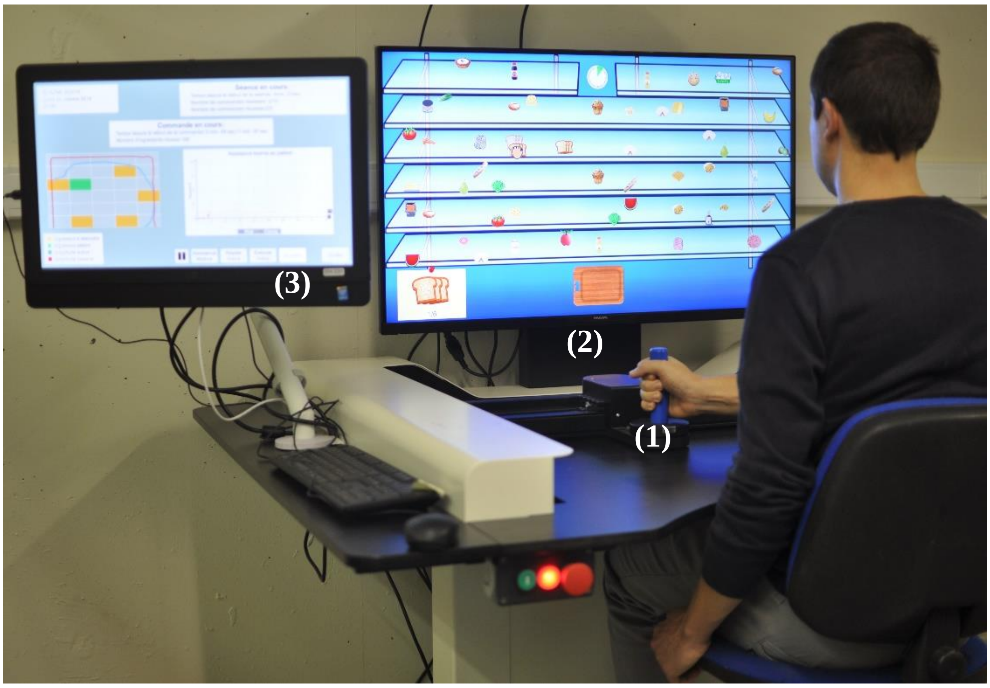


Figure 1. The REAplan® end-effector robot with (1) an end-effector that measures position and force; (2) a monitor for the participant; and (3) a monitor for the experimenter.

6.2.1.2.2 Serious game

The final version of the serious game involves a sandwich shop scenario created for the combined assessment and rehabilitation of hemiparesis and hemineglect (Heins et al., 2017; Chapter 5). The game is developed using Unity Technologies and C***#.*** The game involves a target search and reaching task. Participants assume the role of a sandwich shop owner, and the game involves three steps (Figure 2). The participants first receive a sandwich order of several ingredients from a customer (1). They then have to find the ingredients, one by one, on a shelf containing a variable number of ingredients, some present in the customer's order (i.e., targets), and some not (i.e., distractors) (2). As soon as they perceive the target object, they have to reach to the target and bring the ingredients, one by one, to a chopping board using the handle of the robot. In the third step, they give the order to the customer (3), and receive a score (i.e., stars) depending upon the time taken to complete the order. A reminder of the current ingredient to be reached is always present on the bottom of the shelf. This reminder is placed on the ipsilesional side of the patient. The ingredients on the shelf are organised using an invisible grid of five columns (i.e., two left, one central, two right) and six rows. One grid cell contains a maximum of five ingredients. A maximum of 145 ingredients is presented, with one grid cell used to display a timer. The target ingredients are always presented in the central position of the grid cell. Everyday life virtual objects are used for targets and distractors.

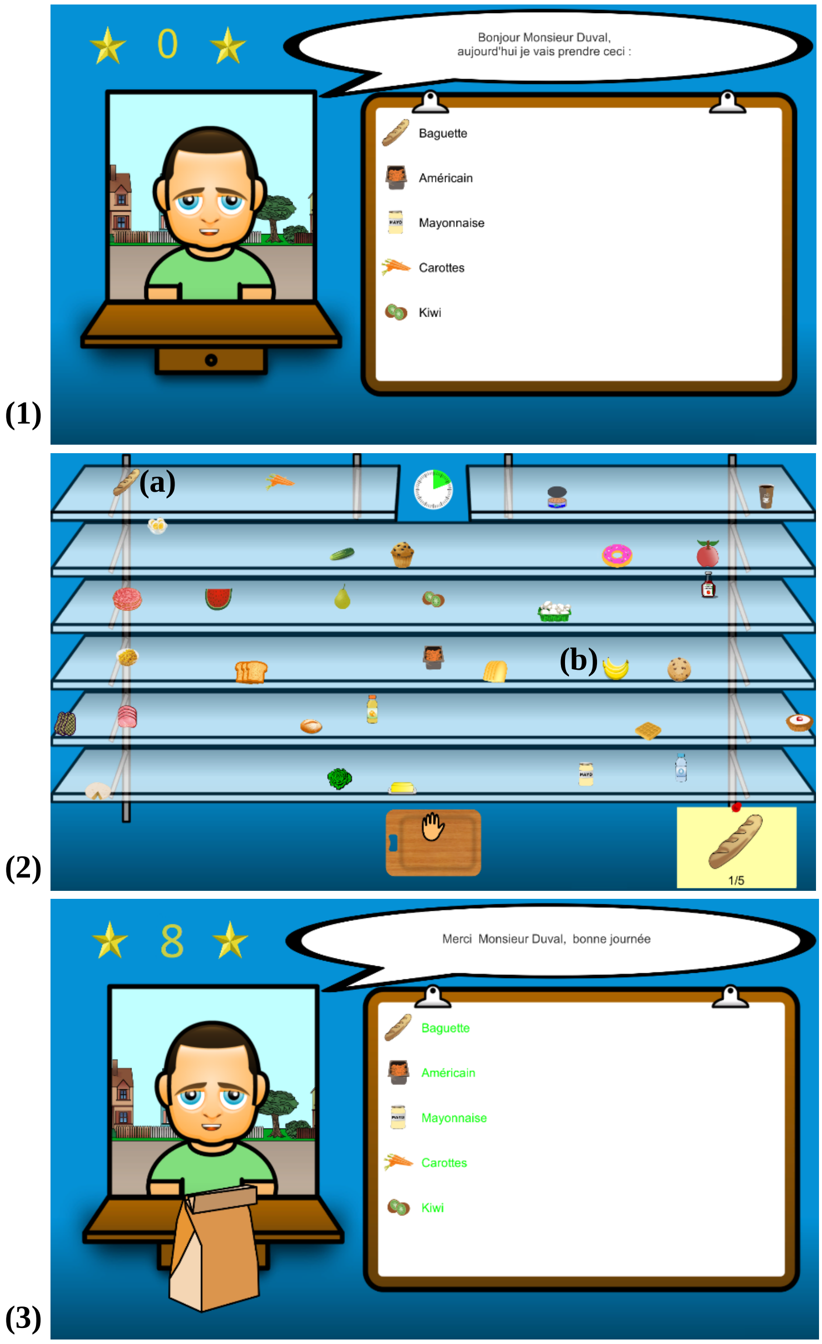


Figure 2. The final sandwich shop game. (1) The participant first faces the customer who gives an order. (2) The participant turns to a shop shelf containing lots of different ingredients. This includes (a) ingredients that are in the order, and (b) distractors. The participant has to select the ingredients in order to make the sandwich, and when complete, (3) they turn back to the customer, and receive a score of achievement based on the time taken to make the sandwich.

For Experiment 1, the functioning of the sandwich game was slightly modified to control some parameters (labelled in this paper as the modified sandwich shop serious game; Figure 3). The aim was to manipulate the amount of presented ingredients. Four levels of attentional load were defined, with 0, 48, 96 or 144 distractor ingredients presented in addition to a single target ingredient (Figure 4). Participants were instructed to move the end-effector of the robot to reach the target as soon as perceived (i.e., correct response). A timer was present in the centre of the shelf indicating the maximum time (2 min 30) to find and bring the target to the chopping board. If participants did not respond within this time limit, the target was considered as omitted. Each trial was separated by a central fixation cross (1000 ms) and by a reminder of the target ingredient placed in the centre of the screen (2000 ms) (Figure 3).

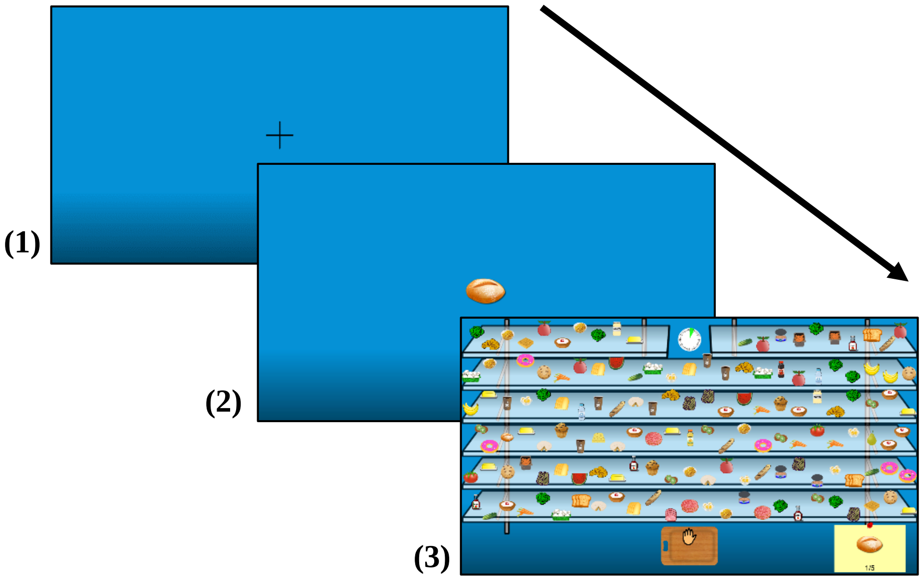
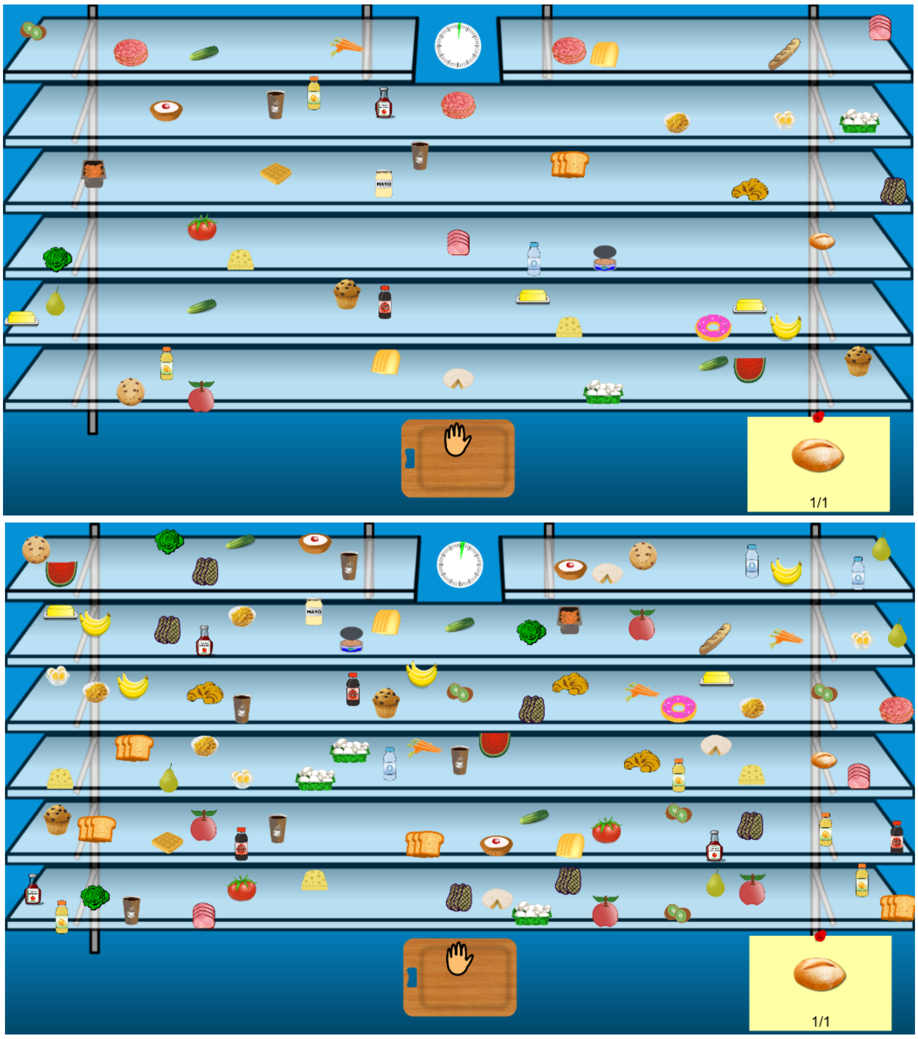


Figure 3. Trial sequence of the modified sandwich shop serious game in Experiment 1 and 2. (1) The trial starts with a fixation cross (1000 ms); (2) the fixation cross is replaced by a target ingredient (2000 ms); and (3) the shop's shelf is presented with one target and one level of attentional load (in this example 144 distractors). The participant is asked to reach to the target as soon as perceived.

The same target ingredient was used for all trials, a round bread loaf, in order to avoid that the participant would mistake an ingredient that was a target in a previous trial, but then became a distractor in the current trial. The distractor ingredients (e.g., pear, tomato, croissant, cheese, bottle of water, coffee) were positioned randomly across the invisible grid, whereas target position was presented randomly across the five columns, in either the second, fourth or sixth row of the invisible grid, making 15 trials per level of attentional load. In addition, one catch trial (i.e., a trial without any target ingredient) for each level of attentional load (except for the level without any distractor) was presented to control for impulsive responses. This lead to a total of 63 trials per participant. Practice trials were given to the participants to increase familiarity with using the robot device and the game. A break was given in the middle of testing, and further breaks given if needed.



(1)

(2)

Figure 4. Attentional load levels in Experiment 1. (1) An example of a display with one target and 48 distractors; (2) An example of a display with one target and 96 distractors.

6.2.1.3 Procedure

The testing lasted 30 minutes and took place in the laboratories of the Faculty of Psychology at the Université catholique de Louvain. After having signed the written informed consent, the position of the participants was standardised. They were placed in a chair without wheels, approximatively 52 cm in front of the REAplan® participant's monitor (visual angle of 84°). The starting position of the robot end-effector was centred on the edge of the horizontal plane and corresponded to the participant's body midline. The height of the robot horizontal plane was adjusted to the participants' height (using a motorised table height adjustment). The participants' feet were placed on the ground, and when necessary, a footrest was used. Participants were asked to use their dominant hand for responses. After receiving the instructions and performing the practice trials, participants began the modified sandwich shop game (Figures 3 & 4). During testing, the experimenter was attentive to the participants' behaviour and took note of any disturbances.

6.2.1.4 Data analyses

Statistical analyses were performed using SPSS software (IBM, SPSS statistics 25). The dependent variable was reaction time of correct target trial responses (i.e., time between the presentation of the shelf containing the ingredients and the participant's initiation of the movement; ms). Reaction time was transformed in natural logarithm (ln) to fit with a normal distribution. A generalized linear mixed model was used for the analysis, with Attentional load (i.e., 0, 48, 96 or 144 distractors) as a fixed effect and Participants as a random factor. Attentional load was considered as a continuous variable and used to measure the linear relationship between reaction time and the number of distractors. In the analyses, no distinction between left and right hemifield was made since no lateralised difference in performance was expected for healthy participants.

6.2.2 Results

Results showed that participants made 99.8% correct responses. A significant linear equation was found ($F(1,1196)= 976.41$, $p<.001$). Participants' predicted ln reaction time was equal to $7.3 + 0.013 * \text{attentional load}$, indicating that participant's ln reaction time increased by a factor of 0.013 ms for each distractor element adding to attentional load (i.e., from 0 to 145 distractor ingredients).

6.3 Experiment 2: Influence of cue efficacy on game difficulty

Experiment 2 investigated how different cues reorient attention to detect targets in contralesional space in hemineglect patients. Cues are commonly used in hemineglect rehabilitation (Kerkhoff, 2001). The majority of cues used for hemineglect therapy are visual cues, such as coloured strips on the extreme contralesional part of the sheet which are reduced gradually as the patient improves (Bowen & Wenman, 2002; Cherney, Halper, & Papachronis, 2003). The degree of attention reorientation depends on the cue salience characteristics (e.g., colour, motion, luminance) (Nothdurft, 2002). Butter and Kirsch (1995) showed that visual dynamic cues (e.g., a flickering light) presented on the contralesional side of space considerably increased reorientation of attention causing reduced hemineglect symptoms. Research has also demonstrated that visual circular cues around the edge of a target are effective to attract attention, with a better efficacy of small and close to target cues in contrast with large and further ones (Nothdurft, 2002). To a lesser extent, auditory cues, either verbal or non-verbal sounds, have also shown encouraging results in reorienting attention in hemineglect patients (Fanthome et al., 1995; Hommel et al., 1990). Limb activation or spatial motor cues where patients move their contralesional limb in contralesional hemispace are another form of non-visual cues reducing hemineglect (Kalra, Perez, Gupta, & Wittink, 1997; Robertson, McMillan, MacLeod, Edgeworth, & Brock, 2002).

Based on these findings in the literature, Experiment 2 tested visual, auditory and haptic cues. Visual cues were selected based on three characteristics: dynamic versus static; targeted (spatially close to the target) versus non-targeted (in the area of the target, but not spatially close); coloured versus non-coloured.

6.3.1 Methods

6.3.1.1 Participants

Patients were recruited from the neuropsychological, and physical medicine and rehabilitation departments of the Cliniques universitaires Saint-Luc and the Centre Hospitalier Neurologique William Lennox in Belgium. Patients were selected according to the criteria: (1) first diagnosis of ischemic or haemorrhagic stroke; (2) clinical diagnosis of hemineglect (e.g., paper and pencil tests such as the Bells Test); (3) good understanding of task instructions; and (4) ability to voluntarily move the end-effector of the REAplan® robot with their non-hemiparetic limb. Patients with orthopaedic illness limiting upper limb function, diagnosis of neurodegenerative disease or any other neurologic conditions were excluded.

Eleven hemiplegic stroke patients (three females) were selected (Table 1). Patients were all right-handed, aged from 38 to 73 (mean age (SD) = 57.7 (12.1)) and between 2 to 40 months post-stroke-onset (mean post-onset (SD) = 15.1 (13.9)). All participants volunteered to participate to the study and provided written informed consent in accordance with a research protocol approved by the Saint-Luc Biomedical Hospital-Faculty Ethics Committee. The study was registered at ClinicalTrials.gov (NCT02543424).

Table 1. Patient demographic characteristics.

Patient	Gender	Age	Lesion	Months post-onset
1	M	69	Left haemorrhagic parieto-occipital stroke	40
2	M	73	Left haemorrhagic lentiform nucleus stroke	6
3	M	53	Right ischemic middle cerebral artery stroke	14
4	M	65	Right ischemic middle cerebral artery stroke	36
5	M	66	Right ischemic middle cerebral artery stroke	5
6	M	38	Right ischemic middle cerebral artery stroke	2
7	M	63	Right ischemic middle cerebral artery stroke	26
8	M	68	Right haemorrhagic thalamic stroke	4
9	F	48	Right haemorrhagic lentiform nucleus stroke	23
10	F	52	Right ischemic middle cerebral artery stroke	6
11	F	40	Right ischemic middle cerebral artery stroke	4

Note: M= male; F= female.

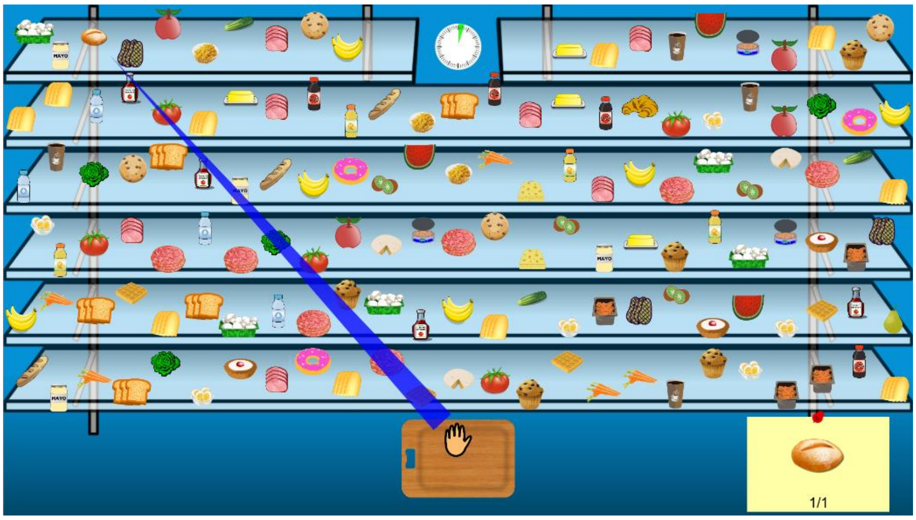
6.3.1.2 Materials

The same apparatus was used as that described in Experiment 1 (Figure 1).

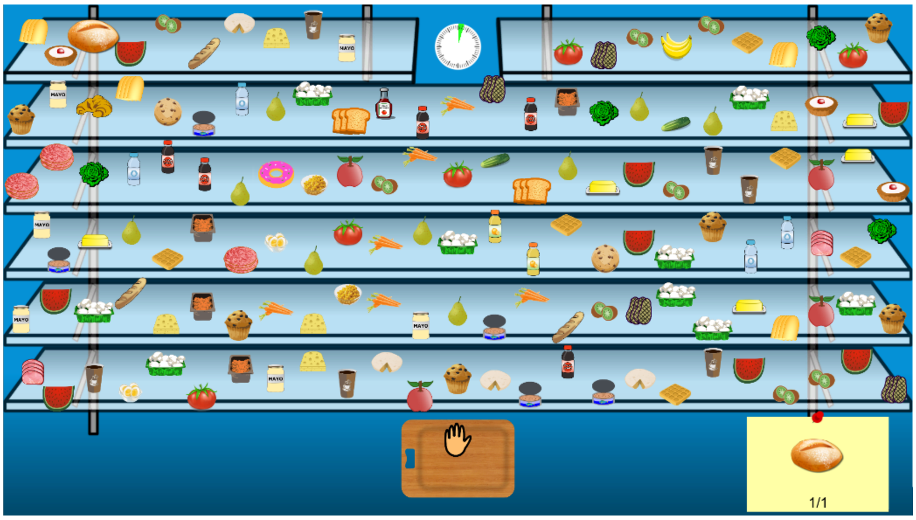
Concerning the cues, one auditory, one haptic and six visual cues were selected (Figure 5). The auditory cue consisted of a voice indicating whether the target was in the left, central or right part of the screen. The haptic cue corresponded to the robot assistance guiding the patient's upper limb towards the position of the target. Note that for this cue, the robot ran in passive mode (see Materials Experiment 1). All the visual cues corresponded to at least one of three characteristics described in the sub-introduction: dynamic/static, targeted/non-targeted, coloured/non-coloured. The visual cues were: (1) a blue static edge surrounding the edge of the target; (2) a blue static column (non-targeted) cueing attention to the vertical area of the target; (3) a blue dynamic column, like visual cue 2, but flashing at 1Hz; (4) a non-coloured static size change of the target (made bigger than the distractors); (5) a non-coloured dynamic size change, like visual cue 4, but where the target dynamically changed size (flashing bigger and smaller at 1Hz); and (6) a blue dynamic arrow (non-targeted) that pointed in the direction of the target. A condition where no cue was presented was used as control condition. Therefore, there were a total of nine conditions (i.e., 8 conditions with cue and 1 control condition without cue).

Experiment 2 used the modified sandwich shop serious game described in Experiment 1 (Figure 3), except that attentional load was set to the maximum level (144 distractors), the target search was facilitated by the presence of a cue, and there were five catch trials. Only one cue was presented per trial, and the different types of cues were randomly selected. Cues were presented at the onset of the trial until the initiation of the reaching movement made by the patient in the direction of the target. This experiment comprised 140 trials per patient (i.e., 15 trials per condition and 5 catch trials).

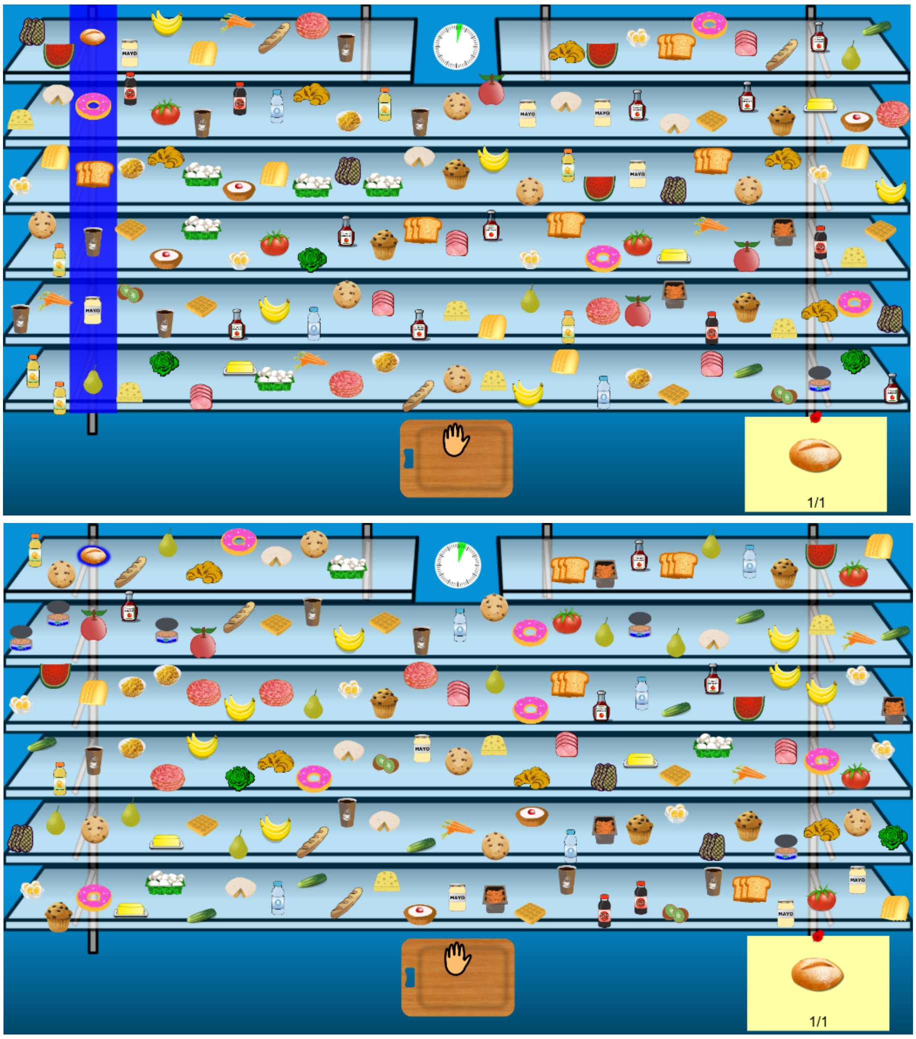
Before the testing, practice trials presenting the different cue conditions were administered to the patients to accustom them to the robot tool and to the game's instructions. A break was provided in the middle of the testing, and patients were informed that they could ask for an additional break at any time.



(1)



(2)



(3)

(4)

Figure 5. Examples of different visual cues in Experiment 2: (1) blue dynamic arrow; (2) static size change; (3) blue static column; and (4) blue static edge.

6.3.1.3 Procedure

The procedure was the same as Experiment 1, except that the testing was divided into three sessions of 30 minutes. Patients performed the testing with their ipsilesional hand.

6.3.1.4 Data analyses

The two left and two right columns of the sandwich shop's invisible grid (see Materials Experiment 1) were recoded as contralesional and ipsilesional columns according to the patient's lesion side. The central column remained neutral. The dependent variable was reaction time of correct target trial responses (i.e., time between the presentation of the shelf containing the ingredients and the participant's initiation of the movement; ms).

Statistical analyses were performed using SPSS software (IBM, SPSS statistics 25). Reaction time was transformed in natural logarithm (ln) to fit with a normal distribution. A generalized linear mixed model was used for reaction time analysis with Cue type (9 conditions), Space (contralesional/central/ipsilesional) and Cue type by Space interaction as fixed effects, and Participants as a random factor. For post-hoc analyses, sequential Bonferroni correction was applied in pairwise comparison ($p < .05$), and Mean (M) and Standard Error (SE) were reported.

6.3.2 Results

Overall, the results showed that 98% of trials were correct responses (no cue: 98.2 %; auditory cue: 95.2%; haptic cue: 95.8%; static size change cue: 98.8%; dynamic size change cue: 99.4%; blue static edge cue: 98.2%; blue static column cue: 100%; blue dynamic column cue: 98.2%; and blue dynamic arrow cue: 98.2%).

Data analysis showed a main effect of cue type ($F(8, 1.4)= 79.8$, $p< .001$). Post-hoc comparisons showed that all cue conditions were significantly different from the control condition without cue. The haptic and auditory cues were not different from one another, but they were significantly different from all other cue types. The different visual cues showed a mix of results that are summarised in Table 2. Analyses also showed a main effect of space ($F(2, 1.4)= 95.4$, $p<.001$). The reaction time for targets presented in the contralesional space (M= 8.6, SE= 0.13) was significantly slower than reaction time for targets presented in central (M= 7.9, SE=0.14) and ipsilesional space (M= 7.9, SE= 0.13). No difference was found between the central and ipsilesional space.

The analyses revealed a significant interaction between cue type and space ($F(16, 1.4)= 3.9$, $p<.001$). Our interest was the influence of the different cue types in the contralesional hemispace (Table 2). Therefore, the post-hoc analyses for central and ipsilesional space are not reported. Post-hoc comparisons for targets presented in the contralesional hemispace revealed that the condition without cue was responded to significantly slower than all other conditions (Figure 6). Among the cue conditions, the results distinguished two groups of cues (Figure 6). The first group included the blue dynamic column, blue static column, blue dynamic arrow and dynamic size change, all not significantly different from each other, but significantly different to the second group of cues. The second group consisted of the auditory, haptic and static size change cues, again with each cue in the second group not significantly different from each other. The first group of cues had a bigger influence on the reorientation of attention to the contralesional side (hereafter named strong efficacy group) than the second group of cues (hereafter named low efficacy group). This was demonstrated by quicker reaction times in the strong efficacy group than in the low efficacy group. Note that the blue static edge cue did not clearly fit in either of the two groups as it demonstrated non-significant differences with cue types in the low efficacy group (i.e., static size change) and with cue types in the strong efficacy group (i.e., blue static column and dynamic size change).

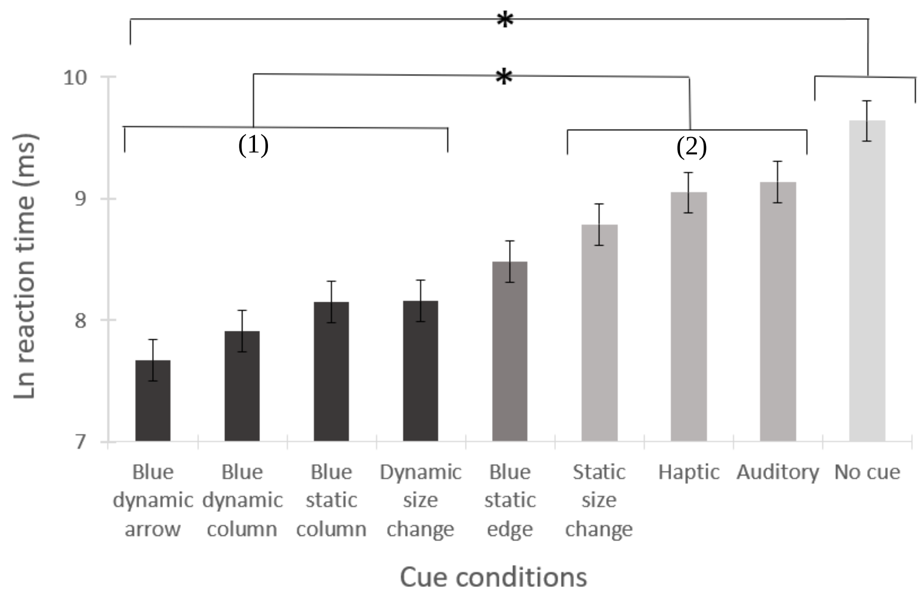


Figure 6. Ln reaction time (ms) for targets in the contralesional hemispace in function of the cue condition with (1) the strong efficacy group, and (2) the low efficacy group. Error bars represent one Mean Standard Error.

Table 2. P-values of post-hoc comparisons for the main effect of cue type and for the interaction between cue type and contralesional hemispace.

Main effect / **Contralesional space**	No Cue **(9.4 (0.15))**	Auditory **(8.7 (0.15))**	Haptic **(8.5 (0.15))**	Static size change **(8.1 (0.15))**	Dynamic size change **(7.6 (0.15))**	Blue static edge **(7.9 (0.15))**	Blue static column **(7.7 (0.15))**	Blue dynamic column **(7.6 (0.15))**	Blue dynamic arrow **(7.6 (0.15))**
No Cue **(9.6 (0.17))**	/	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Auditory **(9.1 (0.17))**	**.012**	/	.105	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Haptic **(9.1 (0.17))**	**.001**	1.000	/	**.000**	**.000**	**.002**	**.000**	**.000**	**.000**
Static size change **(8.8 (0.17))**	**.000**	.205	.501	/	**.000**	.159	**.000**	**.000**	**.000**
Dynamic size change **(8.2 (0.17))**	**.000**	**.000**	**.000**	**.001**	/	**.020**	1.000	1.000	1.000
Blue static edge **(8.5 (0.17))**	**.000**	**.000**	**.002**	.288	.261	/	.159	.051	**.030**
Blue static column **(8.2 (0.17))**	**.000**	**.000**	**.000**	**.000**	1.000	.240	/	1.000	1.000
Blue dynamic column **(7.9 (0.17))**	**.000**	**.000**	**.000**	**.000**	.501	**.002**	.501	/	1.000
Blue dynamic arrow **(7.7 (0.17))**	**.000**	**.000**	**.000**	**.000**	.095	**.000**	.105	.985	/

Note: significant results (p<.05) are shown in bold; (Mean (SE)) are in Ln (ms).

6.4 Discussion

The use of serious games in rehabilitation provides a means to raise patient interest, maintain engagement, and personalise training according to the patient's performance by manipulating parameters such as task difficulty, duration and frequency (Gouaïch et al., 2012; Tomé et al., 2014a). In this paper, two experiments were performed to establish methods to objectively auto-adapt rehabilitation serious game difficulty in accordance to a hemineglect patient's individual performance.

Results on attentional load manipulation with healthy participants in Experiment 1 confirmed our hypothesis, demonstrating that reaction time followed a significant linear increase with increasing numbers of distractor elements in the game. This finding is supported by research in the literature made with brain-damaged patients, where increasing attentional demands through stimuli complexity, numbers of stimuli, or dual tasks, all exacerbate hemineglect impairment (Bonato & Cutini, 2016; Bonato, Priftis, Marenzi, Umiltà, & Zorzi, 2010; Kaplan et al., 1991). For example, Kaplan et al. (1991) showed that in a cancellation task, hemineglect patients cancelled significantly less targets as the number of distractors increased, indicating a linear increase of hemineglect deficit on the contralesional hemifield with increasing distractor attentional load.

The linear equation obtained in Experiment 1 describes the link between reaction time and attentional load, and can now be integrated into a serious game to objectively adapt game difficulty. Here, we illustrate how this equation could be used. At the beginning of a game, the patient could perform the game with the minimum attentional load. For this level of attentional load (z), a desired performance can be defined (y). For example, the patient's reaction time should be one standard deviation from mean control participants' reaction time with the same level of attentional load. The patient's reaction time is recorded (x) and compared to the desired performance (y). If the patient's actual performance (x) is equal to the desired performance (y), the attentional load level remains the same for the subsequent game trial. If the performance (x) is slower or quicker than the desired performance (y), the level of attentional load should be adapted; either increased or decreased following the linear equation. The difference in reaction time between the performance (x) and the desired performance (y) could be calculated and used in the equation to determine the new amount of distractor elements needed for the subsequent game trial (z_n). Since this is an automatic regulation model, the whole process repeats itself for each subsequent trial, and over the repetitions, the patient's performance is continuously updated (x_n) and trends towards the desired performance (y_n). This adaptive model serves to automatically increase game difficulty in accordance to the change in performance shown by the patient until the patient performs at the desired performance for the maximum attentional load.

Results on the cue type analyses in Experiment 2 confirmed the presence of hemineglect in our patient group, with slower reaction times for contralesional than centre or ipsilesional side targets. Our analysis also confirmed our hypothesis, showing evidence that presenting a cue significantly reduced the time by which hemineglect patients could find the target compared to the control condition without a cue. The results showed an interaction between cue type and space, indicating that the efficacy of cue was relative to the side of space where the cue was presented. For analysis of contralesional (neglected) space, which was our main interest, cues could be separated into two groups, confirming our hypothesis suggesting that cue types demonstrate different levels of efficacy (Figure 6). The auditory, haptic and static size change cues were part of a low efficacy group and the blue dynamic and static columns, the blue dynamic arrow and the dynamic size change cues were part of a strong efficacy group. Since the blue static edge cue was not distinctly associated to one group, it was not included in the cue separation. Our results are in line with previous results showing that cue salience is beneficial for attracting attention (Kerkhoff, 2001; Nothdurft, 2002). Further, our results replicated Butter et al. (1990), who suggested that dynamic cues significantly reduced hemineglect compared to static cues, with all dynamic cues presented in the current study considered as strong cues. Contrary to dynamic cues, colour and targeted (close versus distant) cue characteristics did not appear to predict cue efficacy in reorienting attention in hemineglect patients over and above the general benefit between cues when compared to no cue.

The two groups of cues highlighted in Experiment 2 could be integrated into a serious game to objectively moderate difficulty according to hemineglect severity. Here, we describe an example of how these cues could be used. Prior to the game, the patient should perform an initial evaluation without cues. This calibrates the patient's perception across space (x), with targets perceived quickly in certain portions of space and slowly in others. A desired performance can be defined (y).
The perception ability (x) is compared to the desired performance (y) for each portion of space ($\frac{y}{x}$). The portions of space demonstrating better perception ability than the required performance ($\frac{y}{x} < 1$) will not receive a cue during the game, whereas the portions of space demonstrating a lower perception than the required performance ($\frac{y}{x} \geq 1$) will receive a cue. The distance between the perception (x) and the required level of performance (y) will define if the presented cue will be a cue from the low or strong efficacy group. For example, the low efficacy group of cues helps on average two times more than the no cue condition ($\frac{\text{No cue reaction time}}{cue\ reaction\ time}$), while the strong efficacy group helps on average five times more. Therefore, the group of cues that brings performance (x) closer to the desired performance (y) will be selected. Within the selected group of cues, the presented cue can be chosen randomly. During the game, if the target is located in a portion of space needing a

cue, the adequate cue will be displayed. The patient's perception across space will be continuously updated (x_n) during the game, taking into account the reaction time needed to perceive the target (for omissions the reaction time corresponds to the time limit) and cue necessity (i.e., no cue, low or strong efficacy) in order to train performance towards the desired performance (y). This regulation process will allow to automatically adapt game difficulty following changes in patient performance, until the patient performs at the desired performance without receiving a cue.

To optimally auto-adapt game difficulty to the patient's need, it is important to keep in mind that the desired performance (y) has to be challenging for the patient (Perry et al., 2011). To keep the patient motivated, avoid frustration and maintain improvement in the rehabilitation, it is crucial to have a good balance between the success of the patient in the game and the game difficulty (see Cameirão, Bermúdez I Badia, Duarte, & Verschure, 2011; Gouaïch et al., 2012). The great advantage of this type of adaptive rehabilitation method is that the serious game can be made suitable for all degrees of hemineglect severity and for all stages of recovery.

The two experiments ran in this paper allowed for the definition of personalised and objective auto-adapted methods to continuously moderate hemineglect game difficulty, by linearly adjusting attentional load and providing adequate cues to orientate attention to the contralesional hemifield. Future studies will test both types of regulation within the final sandwich shop game (Figure 2) to confirm that game difficulty changes according to the patient's performance. Further, a clinical trial will assess the efficacy of the methods to reduce the hemineglect impairment. Furthermore, a combined regulation of attentional load and cue types could be defined to test if the combination of regulators brings new advantages to patient treatment and recovery efficacy. Authors keen to develop auto-adapted hemineglect rehabilitation should follow similar methods to objectively define how to moderate difficulty in their own game.

Chapter 7

General discussion

Chapter 7

General discussion

The introduction of this thesis (Chapter 1) provided an overview of hemineglect, a heterogeneous condition that can affect different modalities and frames of reference. Given the various manifestations of the condition, comprehensive evaluation is needed. However, the majority of existing hemineglect assessments concern visuo-spatial egocentric hemineglect. Considerably less attention has been paid to visuo-spatial allocentric hemineglect and action impairments in hemineglect. Moreover, time pressure often constrains therapists to make a choice for the most relevant tests rather than using a comprehensive series of tests. Concerning treatment of the condition, various techniques have been developed, but again they are largely for egocentric hemineglect and not for the other types. The presence of the condition remains a long-term problem for patients and influences functional remission years post-onset. Additionally, the functional impairments caused by hemineglect is frequently worsened by the presence of hemiparesis. However, the mutual influence of both deficits has not yet been clearly investigated.

The aim of the present thesis was therefore to make a step forward in the assessment, rehabilitation and understanding of hemineglect through innovations in perception and action measures. Firstly, we wanted to provide a sensitive measure that allowed for a comprehensive assessment of visuo-spatial hemineglect and associated action kinematics. Secondly, we wanted to provide an innovative hemineglect rehabilitation using an auto-adapted serious game that combined perception and action. Finally, we wanted to enlarge the understanding of the hemineglect condition by investigating factors that modulate links in perception and action in hemineglect.

In the following sections, first, a summary of each of the empirical thesis chapters will be given (Chapters 2-6). Then, the three main objectives of the thesis will be discussed relative to the current scientific literature. Finally, the thesis limits and future perspectives will be presented.

7.1 Summary of the thesis

The objective of Chapter 2 was to develop and validate an innovative robot test, the MonAmour, combining the evaluation of visuo-spatial egocentric and allocentric hemineglect. The MonAmour test is a target search task where participants have to find a musical conductor target among musical instrument distractors, and provide a pushing or pulling response on the robot end-effector depending upon the target type (i.e., complete or incomplete). In Chapter 2, we validated the pushing version of the

MonAmour test on post-stroke patients (with and without hemineglect), comparing results to three standardised tests; the Bells test, the Apples test and the Neglect subtest of the TAP. We also analysed the reliability of the MonAmour on a subset of the patient sample, and finally we created norms from test performance with healthy control participants. For egocentric hemineglect, results showed strong correlations between patients' performance on the MonAmour test and on the standardised tests, an excellent sensitivity and reliability, and a good specificity. For allocentric hemineglect, the correlation between the MonAmour and the Apples test was strong, and specificity was good. However, for different reasons explained in the discussion of Chapter 2, the sensitivity and reliability need to be retested. In addition to asymmetric measures to quantify hemineglect, the MonAmour provided valid and reliable measures of non-lateralised impairments, extending its value. In conclusion, the MonAmour test offers a new possibility to simultaneously assess different forms of hemineglect through sensitive measures, providing immediate comparison to norms, reducing learning effect and allowing for a standardised test administration in order to better assess hemineglect and adequately guide rehabilitation.

The aim of Chapter 3 was to extend Chapter 2 and deepen the evaluation of hemineglect patients by measuring visually guided reaching action kinematics for both hands in comparison to healthy control participants. Action kinematics were assessed using two adapted versions of the MonAmour test, differing in attentional load: the MonAmour reaching test and a control reaching test. The MonAmour reaching version was identical to the MonAmour pushing version used in Chapter 2, but required a reaching response towards the target or the musical stand depending upon the type of target, instead of making a pushing or pulling response. The control reaching test was identical to the MonAmour reaching test, but without distractors (thereby having less attentional load) and only presenting complete targets. We hypothesized that, compared to controls, action kinematics of hemineglect patients would show biases when reaching towards the contralesional relative to ipsilesional hemispace, with greater biases in the test with than without attentional load (Experiment 1). We also predicted no difference between hands, with both hands showing lateralised action kinematics in hemineglect patients compared to controls (Experiment 2). Results of Experiment 1 confirmed our hypotheses for the reaction time, but not for the other action kinematics. There was greater slowness for targets in contralesional relative to ipsilesional hemispace, and relative to controls who showed no difference in reaching right or left parts of space. Additionally, as hypothesized, this contralesional bias in reaction time was greater on the MonAmour reaching test displaying distractors (attentional load) than on the control reaching test (no attentional load). Results of Experiment 2 also confirmed our hypothesis showing no difference between hands, both hands demonstrating a lateral bias towards contralesional relative to ipsilesional targets. These results suggest that, at least for our patient sample, the hemineglect condition seems to affect action planning processes, regardless of the hand used but influenced by attentional load. A general slowness observed in hemineglect patients compared to healthy control participants on all the action kinematics variables could not be explained by a deficit specific to hemineglect, as the effect did not interact with the lateral bias. However, this should be confirmed in future studies with stroke patients without hemineglect.

The aim of Chapter 4 was to understand whether upper limb motor weakness influences visuo-spatial perception in stroke patients. We compared healthy control participants and hemiparetic stroke patients, with or without hemineglect using the MonAmour pushing (Chapter 2) and reaching (Chapter 3) versions of the test. Based on embodiment theory, we hypothesized that both patient groups would demonstrate a contralesional relative to ipsilesional space bias, in comparison to healthy participants. We also predicted that the bias would be greater in patients with hemineglect, and we postulated that the reaching response will further increase the contralesional bias. Results confirmed our hypothesis showing that both patient groups were slower to react to targets in contralesional relative to ipsilesional space, and relative to healthy control participants. However, for omissions, only patients with hemineglect demonstrated a contralesional bias. Both versions of the test differed in reaction time, with the MonAmour reaching test being slower than the MonAmour pushing test, but without demonstrating a bigger lateralised bias, which was in contrast to our hypothesis. The lateralised slowness observed in patients without hemineglect can be interpreted in terms of embodiment. However, future investigations need to be run in a larger controlled sample taking into account hemiparesis severity.

The first aim of Chapter 5 was to review the development of a combined motor and cognitive serious game, the ROB*i*GAME, focusing on hemiparesis and hemineglect rehabilitation. The second objective was to run a feasibility study addressing the usability of the game on patients and therapists. The ROB*i*GAME, implemented on a robot device, can include several types of games such as pointing, drawings or force applying games. For this first stage, a sandwich shop game involving pointing responses to targets was created. In this game, patients assumed the role of a sandwich shop owner and were asked to prepare clients' orders by reaching towards the required ingredients that were presented among distractors. In order to increase the game difficulty, some distractors looked like targets but with defects, and the patients were instructed not to respond to these objects. Conversely, to help patients find targets, cognitive cues were used. Additionally, to help patients act to the targets, robot motor assistance was triggered. The feasibility study showed that the game was entertaining and that patients were keen to play again, in particular because of the ecological aspects of the game, the realistic behaviour of the clients (e.g., angry face when the order was incorrect) and the variety of challenging distractors. Results also showed that the type of cognitive cues and the parameters of motor assistance needed to be revised and further tested. Moreover, the methods to auto-adapt the game difficulty in correspondence to patient's performance needed better definition.

The objective of Chapter 6 was to define methods to objectively auto-adapt the difficulty of a serious game (i.e., sandwich shop game) for hemineglect rehabilitation in correspondence to the patient's performance / impairment severity. Experiment 1 tested healthy participants and investigated the influence of different attentional load levels (i.e., 0, 48, 96, 144 distractors) on target detection. We predicted that increased attentional load would linearly increase game difficulty. Experiment 2 tested hemineglect patients and investigated the influence of different cues on target detection in contralesional space. We hypothesized that cues would help patients to detect targets quicker in the contralesional hemispace relative to a no cue condition, and that efficacy in target detection would be moderated by cue types. The results for Experiment 1 supported our hypothesis, with reaction time linearly increasing with attentional load. The results of Experiment 2 also confirmed our hypothesis showing that the presence of a cue helped the patient to more quickly find contralesional targets relative to a no cue condition. Additionally, results allowed to rank cues in two different groups depending on their efficacy. The two experiments allow for an objective regulation of game difficulty using a linear equation for attentional load or using cues of different efficacy. The efficacy of these methods to reduce hemineglect should be tested in future studies.

7.2 A comprehensive evaluation of hemineglect

Recent literature argues that existing tests used in the clinic (often referred to as paper and pencil tests), are not sufficiently sensitive for the detection of minor hemineglect impairments (Bonato, 2012; Bonato & Cutini, 2016; Buxbaum et al., 2012; Grattan & Woodbury, 2017; Ogourtsova, Archambault, et al., 2015). Moreover, the heterogeneity of the hemineglect condition makes the diagnosis challenging (Grattan & Woodbury, 2017). Therefore, to obtain a complete evaluation of patients' deficits, several assessments focusing on different hemineglect forms is recommended (Bailey et al., 2000). However, therapists report that the lack of time in clinical practice prevents the administration of a large panel of tests (Petzold et al., 2014). A possible alternative is therefore to use assessments measuring multiples types of hemineglect (Grattan & Woodbury, 2017).

Chapters 2, 3 and 4 were specifically aimed at this objective. Whereas the majority of validated hemineglect tests have focused on one form of hemineglect, especially the egocentric form, the MonAmour test provides a combined visuo-spatial egocentric, allocentric and action kinematics evaluation. The simultaneous evaluation of egocentric and allocentric hemineglect has already received some attention in the literature and in clinical practice, in particular with the Ota and the Apples cancellation tests (Bickerton et al., 2011; Ota et al., 2001). However, to our knowledge, the MonAmour is the first test in which action execution kinematics (i.e., execution time, peak speed, smoothness, straightness, accuracy) can be evaluated at the same time as egocentric and allocentric hemineglect. Although several studies have previously attempted to evaluate visuo-spatial and motor impairments, they mainly relied on accuracy measures such as the side of pointing on a Landmark task or centimetres of deviation on a line bisection task, but without using action execution kinematics (Coslett, Bowers, Fitzpatrick, Haws, & Heilman, 1990; Harvey, Milner, & Roberts, 1995). Similarly, studies that investigated action execution kinematics in hemineglect (e.g., Konczak & Karnath, 1998) did not use tasks measuring visuo-spatial hemineglect (e.g., task with numerous and various distractors).

The future use of the MonAmour test in clinical practice will therefore allow for a comprehensive evaluation focusing both on perception and action responses. As observed in Chapter 3, and in line with some previous studies (e.g., Rossit, Malhotra, et al., 2009), action execution kinematics of egocentric hemineglect patients might not be associated with a lateralised bias. Instead, a general slowness compared to healthy participants was found, which seems to be consistent across different papers reporting kinematics measures (see Ogourtsova, Archambault, & Lamontagne, 2015 for a review). Even if non-lateralised, this impairment is still worthy of measuring and could be re-evaluated during and after rehabilitation to measure and demonstrate general improvements in action. It is also worth noting that there may be evidence of lateralised action kinematics deficits with more testing, perhaps due to different lesion size, side or site (e.g., Mattingley et al., 1994). These further investigations could lead to new discoveries and enrich the action kinematics hemineglect debate. Nevertheless, in absence of difference of action execution kinematics between the hemineglect patient and healthy participants at the initial evaluation with the MonAmour reaching version, the retest of visuo-spatial performance after rehabilitation could be performed with the MonAmour pushing version in order to save time (i.e., approximate duration of 9 and 15 minutes for pushing and reaching versions respectively). Indeed, the results of Chapter 4 showed that the percentage of omissions did not differ between the MonAmour pushing and reaching version, and that reaction time was slower in the reaching version, but did not differ in the detection of the lateralised bias. Note that, to evaluate significant clinical improvements on the MonAmour pushing version, the Minimal Detectable Change (MDC) defined in Chapter 2 could be used between the pre- and post-treatment.

Discrepancies between test performance on clinical measures and everyday life behaviour have been observed in hemineglect, particularly in the chronic stage. For example, patients can bump into a wall after having succeeded hemineglect paper and pencil tests (Ten Brink, 2018). Given the characteristics of the MonAmour test and the results obtained in Chapters 2, 3 and 4, there are good reasons to think that these discrepancies should be reduced when using the MonAmour test. Contrary to paper and pencil tests (e.g., Bells test), the position of the stimuli in the MonAmour test were randomised for each trial, leading to reduced learning effects (Erez et al., 2009). Also, the MonAmour test was displayed vertically spanning a larger visual field that was close to the visual angle used in daily activities such as walking. Moreover, in order to diagnose egocentric hemineglect, the MonAmour test considered the performance in terms of omissions asymmetry as in current paper and pencil tests, but the MonAmour test also measures reaction time asymmetry. The use of reaction time for hemineglect diagnosis was important, as demonstrated in Chapter 4. Although the hemiparesis group did not demonstrate any impairment in omission asymmetry, a contralesional bias was observed on the reaction time measure. In Chapter 2, the combination of these two measures (i.e., omissions and reaction time) demonstrated high test sensitivity and specificity, even better than some recently published computerised and virtual reality assessments (e.g., VRLAT, VR-DiSTRO). Indeed, in Chapter 2 we selected patients having received a clinical diagnosis of egocentric hemineglect by therapists. Interestingly, the MonAmour test detected hemineglect in all but one of the patients (24/25), whereas the paper and pencil tests (i.e., Bells test, Apples test) administered at the same time detected hemineglect in about half of the same patient sample. This suggests that the MonAmour may be more sensitive for detecting hemineglect in acute, but also chronic patients with slight impairments.

Chapters 3 and 4 brought even more precision to the detection of lateralised biases. The MonAmour test considers visual space as a continuum going from the extreme contralesional to the extreme ipsilesional space. As in the study of Smania et al. (1998), this allowed the observation of increasing impairments towards the space extremities, rather than a dichotomous impairment between contralesional versus ipsilesional parts of space. For example, in Chapter 3, for hemineglect patients, a bigger asymmetry on the MonAmour test compared to the control reaching test was observed only for the space extremities (i.e., extreme contralesional and extreme ipsilesional). Moreover, the results of Chapter 3 demonstrated that the detection of lateralised biases across space (i.e., Distance-x) were the same for the ipsilesional and the contralesional hand in hemineglect patients (without hemiplegia). This suggests that hemineglect evaluation could be equally performed by both hands, despite the motor upper limb weakness potentially affecting the contralesional hand.

In addition to the evaluation of lateralised impairments, the MonAmour test provides total omissions and reaction time measures regardless of space. These measures allow for the identification of non-lateralised attention deficits. The results of Chapter 2 showed that the large majority of patients diagnosed as having hemineglect (either egocentric or allocentric) were also impaired on the overall measures compared to norms. As discussed in the review of Husain and Rorden (2003), it is common to have non-lateralised selective or sustained attentional problems that co-exist with hemineglect, which could either exacerbate it or slow down the rehabilitation progress. Also, in our patient sample of Chapter 2, five patients were identified with overall impairment but no egocentric hemineglect, and three with overall impairment but no allocentric hemineglect. Functional imaging studies suggest that lateralised attention relies on the superior parietal lobe, non-lateralised attention relies on the inferior parietal lobe, and that the intraparietal sulcus seem to be involved in both mechanisms. These differences could explain the discrepancies that we found between patients impairments (Husain & Rorden, 2003).

The MonAmour test is an effective tool able to measure and distinguish different forms of hemineglect and associated non-lateralized attentional problems. Such a specific evaluation allows to establish which forms are impaired (and their severity), to define a tailored rehabilitation and to measure improvements linked to each form during treatment (Bowen et al., 1999; Husain & Rorden, 2003; Riestra & Barrett, 2013). Since the success of a rehabilitation seems related to the patient's profile (Buxbaum et al., 2004), it is important to choose the best hemineglect rehabilitation combination for each individual patient (Riestra & Barrett, 2013). On the contrary, a non-specific evaluation could lead to a rehabilitation focusing on only the impairment that was diagnosed (Grattan & Woodbury, 2017) and more likely lead to latent long-term deficits. For example, a treatment for egocentric hemineglect will not necessarily be effective for allocentric hemineglect (Gossmann et al., 2013). Also concerning lateralized and non-lateralized deficits, it is important to know if a patient has both deficits at diagnosis. This will allow the therapist to begin the treatment by focusing first on the non-lateralized deficits, increasing awareness of the impairments, and then facilitate rehabilitation of lateralized deficits (Robertson, Tegnér, Tham, Lo, & Nimmo-Smith, 1995). Specific evaluation is therefore essential to guide personalised therapy.

7.3 An innovative serious game rehabilitation for hemineglect

Many different hemineglect rehabilitation techniques have been created over the past years (Luaute et al., 2006). However, no specific guidelines have been formally established (Ting et al., 2011), possibly due to the heterogeneity of the condition. Moreover, the efficacy of the different therapies is somewhat questionable since hemineglect impairments might persist more than one year post-stroke (Kerkhoff & Schenk, 2012). The use of new technologies allows going beyond conventional rehabilitation techniques and seems promising to improve the patient recovery (Choi et al., 2016; Ogourtsova, Souza Silva, et al., 2015).

Chapters 5 and 6 chart the development of a serious game (ROB*i*GAME) on a robot device for a combined hemineglect and hemiparesis rehabilitation, two major post-stroke deficits that frequently co-occur (Kerkhoff, 2001). In the present thesis, the objective was to define the serious game parameters of the hemineglect rehabilitation. The global aim was to establish a specific rehabilitation for egocentric, allocentric and action kinematics impairments in hemineglect. However, in this first stage, the serious game rehabilitation did not focus on allocentric hemineglect since the diagnosis efficacy of Chapter 2 needs further investigation (see Section 7.5.1). Similarly, the serious game did not concentrate on lateralised action execution kinematics (i.e., execution time, peak speed, smoothness, straightness, accuracy) since no results in this sense were found in Chapter 3. The hemiparesis parameters were the focus of another PhD thesis (Dehem, 2018; the two PhDs funded by the Région Wallonne – WB Health).

The use of a robot device associated with a serious game has the potential to enhance hemineglect therapy in comparison to conventional methods. It brings a greater number of measures (e.g., reaction time, action kinematics, omissions, necessity of a cue) to better follow the patient's perception improvement across space (i.e., from extreme contralesional to extreme ipsilesional) during treatment. Additionally to the types of cues used in standard rehabilitation (e.g., visual cues), the robot also provides an haptic cue that "motorically" brings the patient's hand in the area of the target. Furthermore, as illustrated by the schematic representation of ROB*i*GAME in Chapter 5 (see Chapter 5, Figure 2), hemineglect therapy can be dynamically tailored to each patients' individual performance, taking into account these measures and adjusting the difficulty using objective methods, such as the methods defined in Chapter 6. This type of automatic adaptation has recently demonstrated positive results for post-neurological rehabilitation (e.g., Gouaïch, Hocine, Van Dokkum, & Mottet, 2012).

The innovative ROB*i*GAME rehabilitation for hemineglect was developed based on some principles that demonstrated efficacy in conventional hemineglect therapies. As in visual scanning therapy (Azouvi et al., 2000b), the objective was to increase difficulty progressively, adding more and more distractors in accordance to the success of the patient at the previous exercise. With the aim to moderate difficulty of the serious game, Chapter 6 provided an equation describing the link between reaction time and attentional load (i.e., amount of stimuli presented on the screen) in healthy control participants. This result can now be used to auto-adapt game difficulty to the patient's performance. Since high attentional load has demonstrated to be effective in triggering hemineglect, even in the lighter forms of the condition (Bonato & Cutini, 2016; Kaplan et al., 1991), this method allows rehabilitation from acute to chronic stages, and in the end, until performance equivalent to healthy participants.

A second promising method to moderate difficulty was investigated. The use of cues has shown positive results in attention reorientation in experimental studies (Butter et al., 1990) and in conventional rehabilitation such as visual anchoring points in visual scanning therapy (Luaute et al., 2006) or haptic cue in limb activation therapy (Brunila et al., 2002; Choi et al., 2016; Varalta et al., 2014). In Chapter 5, cues were tested in the rehabilitation serious game. However, the feasibility study showed that the different cues required further investigation. Chapter 6 tested therefore eight cue types including visual, auditory and haptic cues. The results provided a ranking of cue efficacy for the reorientation of attention towards the contralesional hemispace in hemineglect patients. This allowed defining a rehabilitation method that could display a cue of a particular efficacy (low or strong) depending upon the needs of the patient. This goes further than recent rehabilitation serious games, that included cues (Mainetti et al., 2013), but did not define by how much the cues moderated patient's performance.

These methods moderating hemineglect rehabilitation difficulty can be used to reach a good balance between the difficulty level of the game and the patient's performance. This balance is known to maintain engagement and motivation during the therapy (Gouaïch et al., 2012). Moreover, to enhance engagement, a simple but interesting scenario (i.e., sandwich shop owner) was chosen based on a questionnaire survey administered to healthy and post-stroke adults. In this respect, the feasibility study of Chapter 5 reported positive results concerning the enjoyment provided by the game scenario. The engagement was maximized using a positive scoring, providing frequent feedback about the patient's performance and improvements, and using randomised stimuli position giving the patient the feeling that the exercise was always different. As in previous studies, these features bring the patient into a state of complete focus and immersion in the game (Mainetti et al., 2013).

Another great advantage of the serious game developed in Chapters 5 and 6 was that it gave the possibility to start rehabilitation without an evaluation phase, as the game difficulty dynamically adapted to the performance of the individual patient. This brings the considerable benefit of initiating the rehabilitation in the very first stages post-stroke-onset, facilitating rehabilitation within the spontaneous recovery period and potentially amplifying it (for hemineglect up to 3 to 6 months; Cassidy, Lewis, & Gray, 1998; Stone, Patel, Greenwood, & Halligan, 1992). Currently, it has been recommended to begin multidisciplinary rehabilitation (here cognitive and motor) in the first few days following stroke in order to enhance the recovery (Cramer, 2008; Langhorne, Bernhardt, & Kwakkel, 2011). Moreover, since the results of Chapter 3 showed that hemineglect evaluation through reaction time was equivalent for both hands, early rehabilitation with ROB*i*GAME project could focus simultaneously on hemineglect and hemiparesis using the contralesional hand. This could enhance clinical practice, currently lacking means to follow these recommendations.

7.4 A better understanding of hemineglect

This thesis investigated factors that might modulate the link between perception and action, namely attentional load, hand used, motor upper limb weakness, types of response and cue salience. The investigation of these factors enlarged our understanding and knowledge about hemineglect.

Although hemineglect is usually assessed by visual perception based tasks, several studies have investigated visually guided actions in hemineglect (e.g., Heilman et al., 1985; Konczack and Karnath 1998; Rossit, Muir et al., 2009). This literature remains mixed concerning the existence of lateralised biases for actions with the ipsilesional hand. Relative to other studies, our paradigm had the advantage to measure perception and action performance in five different parts of space, going from the extreme contralesional to the extreme ipsilesional space (i.e., Distance-x), with each part of space comprising six vertical target locations. This allowed to measure the gradient deficit across space in hemineglect (Smania et al., 1998). Chapter 3 showed a distinction between action execution kinematics (i.e., execution time, peak speed, smoothness, straightness, accuracy) and reaction time in patients with egocentric hemineglect patients. For all action execution measures, similar to healthy control participants, hemineglect patients did not demonstrate any asymmetry in reaching targets towards contralesional compared to ipsilesional hemispace. Instead, for reaction time, asymmetrical results towards the contralesional compared to ipsilesional hemispace were found in hemineglect patients. These results could be explained by a deficit in action planning responsible for the selection of the target in a spatial location, but a spared control system for action execution (Glover, 2004).

Results in Chapter 6 showed that this action planning deficit towards contralesional targets could be improved by increasing the salience of the target location using a cue. This improvement was modulated by the degree of cue salience, with a better efficacy of dynamic features (see Butter et al., 1990 for similar results). Additionally, the results of Chapter 3 demonstrated that visual attentional load also modulated the action planning impairment in hemineglect patients. Increased attentional load in the MonAmour reaching test caused reduced performance demonstrated by a bigger contralesional reaction time asymmetry than in the control reaching test without distractors. This effect confirms previous results (e.g., Kaplan et al., 1991), and seems in line with the model of Posner and Petersen (1990) that postulated a deficit in the disengagement of ipsilesional stimuli in hemineglect.

This action planning impairment for contralesional targets seems however independent to the type of response required. Chapter 4 showed that reaching responses differed from pushing responses only by slowness in reaction time across all space, probably due to the higher complexity in the planning of the movement. Similarly, Chapter 3 showed that responding with the contralesional versus ipsilesional hand did not influence reaction time for asymmetrical performance. This suggests that, at least in a task where the starting position is identical for both hands, the action planning system may consider the target location relative to the starting position regardless of the hand-effector. This could imply that hemineglect influences higher-order planning before hand selection. This finding showing no hand effect may appear to contradict previous studies showing that hemineglect improves following contralesional limb activation (i.e., limb activation therapy). However, the effect is not contradictory, as the potent effect of limb activation therapy comes from the combination of moving the contralesional limb specifically in contralesional hemispace (Robertson et al., 2002). In the MonAmour, for both hands, the starting position was centred to the patient's body midline.

Interestingly, Chapter 4 reported that the asymmetrical reaction time for contralesional compared to ipsilesional targets was also manifested by stroke patients with motor upper limb weakness without hemineglect. This finding suggests that the action planning deficit discussed earlier seems not specific to the hemineglect condition. We argued that action capabilities influenced perception abilities. More precisely, as in previous studies (Filbrich et al., 2017; Makin et al., 2010), here it was a lateralised action deficit that resulted in a lateralised perception bias. This is in line with the embodiment theory (Coello & Delevoye-Turrell, 2007; Proffitt, 2006), and premotor theory of Rizzolatti and colleagues (1997) whereby space representation is "motorically" constructed and that a lesion in the motor areas leads to a deficit in the neural representation of a specific portion of space. From this result, we suggest that in future experimental studies and clinical diagnosis, the performance of hemineglect patients should be compared to healthy control participants as usual, but additionally to patients with motor weakness without hemineglect. This would subtract the embodied contralesional bias to the hemineglect induced bias, and thereby highlight the actual hemineglect deficit. However, it has to be noted that it is not always easy to make a clear distinction between both types of patients when the deficits are minor.

Additionally to the contralesional bias in reaction time, the results of Chapters 3 and 4 showed a general impairment of hemineglect patients compared to healthy control participants across all space. Concerning omissions and reaction time, the results of Chapter 4 showed that this general reduced performance could not be explained by the motor weakness, because even in the ipsilesional hemispace, hemineglect patients performed significantly worse than patients with only motor weakness. For action execution kinematics, this profile of performance seems in accordance with studies showing impairment of the ipsilesional hand in hemiparesis patients, regardless of the presence of hemineglect (Bustrén et al., 2017; Konczak & Karnath, 1998).

Taken together, the results of this thesis provide evidence that in target search tasks with a fixed central starting position, a distinction can be made between impairments in perception (here, the measures of omissions and reaction time) and in action (here, the measures of action execution kinematics). Moreover, the contralesional impairment in perception seemed to be modulated by the independent variables of cue salience, attentional load and motor weakness, but independent from the type of response required and the hand used. It has to be noted that even if we label the problem as "perceptive", it mainly refers to the underlying attentional process that plays a major role in hemineglect. Evidently, the results and their interpretations have to be taken with caution because of some study limits.

7.5 Thesis limits and future perspectives

The present thesis provided insights in the assessment, rehabilitation and understanding of hemineglect. However, there remains unanswered questions and aspects that could be improved. This section will summarize the main limitations regarding the three objectives of the thesis and suggest possibilities for future research.

7.5.1 Hemineglect evaluation

The results of Chapter 2 showed that the MonAmour test provided a valid and reliable measure of egocentric hemineglect. Concerning the allocentric component of the test, although the results showed a strong correlation and a high specificity with the Apples test, there was a feeble sensitivity (50 %) and an absence of reliability. The weaknesses of the allocentric component of the test could be explained by the low prevalence of allocentric hemineglect (Marsh & Hillis, 2008). Another possible explanation lies in patient recruitment, which was not representative of the allocentric hemineglect population, as most patients were recruited primarily based on the presence and clinical diagnosis of egocentric hemineglect. As claimed by previous studies, brain lesions responsible for egocentric hemineglect may be distinct from the areas causing allocentric hemineglect (Karnath & Rorden, 2012; Verdon et al., 2009). Future studies should therefore confirm the diagnosis efficacy of the allocentric component of the MonAmour test by recruiting patients having signs of allocentric hemineglect diagnosed using appropriate clinical tests (e.g., Apples test).

7.5.2 Hemineglect rehabilitation

Chapter 5 illustrated the schematic representation of the ROB*i*GAME global regulation (see Chapter 5, Figure 2). Chapter 6 defined personalised and auto-adapted methods in order to moderate the game difficulty with attentional load or cue types. However, the limits are that the functioning and efficacy of the game regulation have not yet been tested. The next paragraph proposes a description of how it would be defined and tested.

As described in Chapter 5, the serious game comprises a set of performance indicators (x) that refers to the patient's performance at the previous sandwich trial, and a corresponding set of difficulty indicators (y) referring to the desired difficulty level for the next sandwich trial (Figure 1).

To regulate game difficulty for hemineglect, two performance indicators are used[1]: (1) x_{ego}, referring to the patient's reaction time for each ingredient of the sandwich in function of attentional load and cue type; and (2) x_{time} referring to the time spent doing the entire sandwich in function of the number of ingredients included in the sandwich. The two corresponding difficulty indicators ($y_{ego}; y_{time}$) are defined from the patient's performance during the previous sandwich trial ($x_{ego}; x_{time}$) and from the patient's success rate at the ten previous sandwiches (u). A sandwich is considered as succeeded (u) if completed within the time limit. In order to adapt difficulty, first the success rate and then the performance indicators are compared to a reference.

The success rate reference (u_{ref}) is set to 75% to keep the game challenging, but also to maintain the motivation of the patient throughout the rehabilitation (Cameirão et al., 2010). Therefore, if the patient succeeds on at least 75% of the last ten sandwiches, it indicates that the game difficulty was too easy for the patient and the game difficulty will be increased by 5% for the next sandwich. Instead, if the patient succeeded on less than 75% of the last ten sandwiches, the difficulty level of the next sandwich will be decreased by 5%. With this auto-adapted regulation, patients will continuously be challenged at 75% of their own individual performance. In order to determine which difficulty indicators ($y_{ego}; y_{time}$) have to be increased or decreased by 5% for the next sandwich, the performance indicators (x_{ego}; x_{time}) of the previous sandwich are compared to performance indicator references (x_{refego}; $x_{reftime}$). If only one performance indicator has a bigger error than the tolerated error, this indicator will be modified (i.e., increased or decreased by 5%) and the other one will remain stable. Instead, if both performance indicators have bigger errors than the tolerated error, both indicators will be modified (increased or decreased by 2.5% each).

[1] Note that in the complete version of this serious game, motor impairment is also measured and rehabilitate through lateral and longitudinal assistance (x_{lat}, x_{long}, Y_{lat}, Y_{long}). However, these components of the game will not be detailed in this thesis (Dehem, 2018).

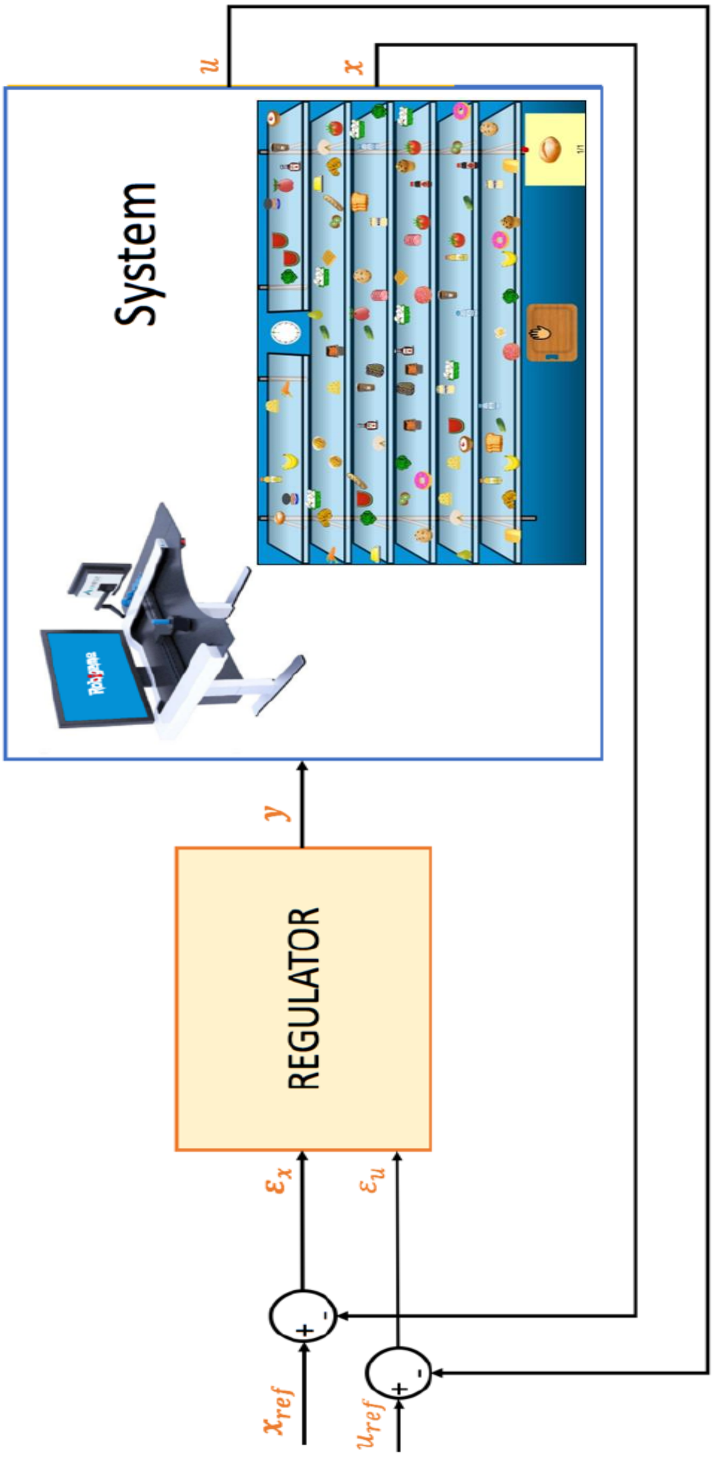


Figure 1. Schematic representation of the regulation of the sandwich shop serious game.

This regulation system has to be tested in order to validate that the difficulty is adapted according to the patient's performance. It should be tested on a large group of hemineglect patients with mild to severe impairments, either with hemineglect severity used as a continuous variable, or by creating two groups of patients with a median split, one group having severe and the other one having mild hemineglect. In the group design, for the group presenting severe hemineglect, the starting level of difficulty indicators (y) should be set at the maximum level. Conversely, for the group presenting mild hemineglect, the starting level of the difficulty indicators (y) should be set at the minimum level. For the severe hemineglect group, the game difficulty should show a progressive decrease during the game, whereas for the mild hemineglect group, the game difficulty should show a progressive increase during the game. In this study, particular attention can also be given to the number of sandwich trials needed to reach the patient's appropriate difficulty level. If adaptation is too long, the regulator should adapt the difficulty with an increase or decrease bigger than 5%.

In the sandwich shop serious game developed in Chapter 5, some of the distractors could correspond to targets with a defect on the contralesional or ipsilesional side (e.g., rotten or damaged). This was included to evaluate and rehabilitate allocentric hemineglect. However, in the present thesis, we could not evaluate or regulate game difficulty based on patient's allocentric hemineglect. In the current game, the patient was instructed to reach to the target without defect, presented on the yellow reminder situated under the shelf (see Chapter 5, Figure 5). If the patient reached the target without defect in presence of defected targets without making false positive errors, it does not necessarily indicate that the patient does not have allocentric hemineglect. It is possible that the patient did not perceived the presence of defected targets because the actual target was immediately detected. Similarly, if the patient makes three false positive errors for one sandwich, and only one false positive error for the subsequent sandwich, it does not necessarily mean that the patient improved. It could be that the patient did not perceive the other defected targets on the second sandwich. To take allocentric hemineglect into account, the game functioning may need revision. As mentioned in Chapter 1, rehabilitation focusing on allocentric hemineglect has never truly been investigated. There is only evidence coming from a single case study suggesting that emphasizing the difference between complete and incomplete targets was beneficial for allocentric treatment (Pachalska et al., 2004). In this sense, the sandwich shop game could comprise an additional task where the patient receives a visit from a food inspector that asks to examine the ingredients and to decide whether or not they have to be thrown into the bin because of the presence of a defect. The patient would be then encouraged to pay attention to the contours of each target, and would receive feedback in correspondence to their performance. Integrating the game regulator, the allocentric difficulty could be evaluated and adapted, displaying targets with defects progressively smaller as the patient improves.

The future hemineglect serious game rehabilitation could benefit from the use of Virtual Reality (VR), which has demonstrated promising results in the literature (Ting et al., 2011). Integrating the sandwich shop game in a VR-system would allow patients to be immersed in an environment that appears similar to a real sandwich shop. The VR-system could be combined with the robot device in order to keep the advantage of haptic feedback, or it could be used on its own, for example with patients only having hemineglect and not hemiparesis. In this latter option, patients would see the customers in front of them and would have to physically turn towards the shelf to search for the ingredients, as they would have to do in real life. To improve space exploration, the shelf could be situated in their contralesional space. The acting hand in real world would be displayed by a virtual hand in the VR. The physical and virtual hand actions would correspond to each other so that patients feel like they are controlling the virtual hand. Moreover, since the VR gives the advantage to match hand action and target location, it would create a more real life experience in the game. The adaptation of the serious game in VR would also enable the addition of new other relevant measures, namely eye and head tracking, providing more information about the patients' visual search pattern (e.g., angle of head rotation, time taken to turn the head). In order to increase engagement and motivation in the therapy, other types of games scenarios using the same regulation parameters as the sandwich shop game could be created (e.g., catching fish of particular varieties presented alongside other distractor fish). Using VR, the game could easily be adapted into a multiplayer game scenario where patients play with a caregiver or a relative. This multiplayer functionality should benefit the quality of therapy by adding a social dimension and engagement to it, as suggested in a recent study on stroke patients (Maier, Ballester, Duarte, Duff, & Verschure, 2014). Finally, given the cost-efficacy of VR-systems and the auto-adaptation of the serious game, patients could extend and intensify their rehabilitation at home.

7.5.3 Hemineglect understanding

Chapter 3 enlarged our understanding of actions in egocentric hemineglect. However, additional investigations are needed to disentangle and confirm which action kinematic profiles are present in hemineglect. The results showed that hemineglect patients had a general reduced performance for all the action execution kinematics (i.e., execution time, peak speed, straightness, smoothness and accuracy) in comparison to healthy control participants. Interestingly, several studies reported the same profile of performance in patients with a motor impairment, but without hemineglect, suggesting that this deficit might not be hemineglect-specific (Bustrén et al., 2017; Konczak & Karnath, 1998; Ogourtsova, Archambault, et al., 2015). Future studies should therefore include a control group of stroke patients without hemineglect to further investigate if in our paradigm, this general reduction of performance is independent from the presence of hemineglect. The results of Chapter 3 also showed that action execution kinematics were not lateralised towards contralesional relative to ipsilesional hemispace in hemineglect. However, the hand-start position has been found to be critical in the assessment of action kinematic deficits (Duhamel & Brouchon, 1990; Mattingley et al., 1994). Accordingly, two additional starting positions could be integrated to the MonAmour reaching test, one on the contralesional side (i.e., distance 20) and one on the ipsilesional side (i.e., distance 60). This new paradigm would provide additional insights into better understanding actions in hemineglect. For example, would action execution kinematics be lateralised when the target is presented in the same hemispace as the starting position? Or would action execution kinematics be lateralised when the target is in the opposite hemispace, requiring crossing the patient's body midline? Finally, since the study of Mattingley et al. (1994) demonstrated action kinematic deficits in patients presenting severe hemineglect (compared to less severe), it could be important to investigate whether the results of Chapter 3 would differ depending upon hemineglect severity.

Chapter 4 showed the presence of a contralesional bias on reaction time in patients with motor weakness and hemineglect, but interestingly also in patients with only motor weakness (and no hemineglect). It was suggested that the action capabilities could have had an influence on the perception abilities as claimed by embodiment theory (Proffitt, 2006). However, this hypothesis needs to be further confirmed. In future studies, the inclusion criteria of patients should use sensitive measures and brain imaging in order to have supplementary evidence that patients with motor weakness do not have lesions in areas highly correlated with the occurrence of hemineglect (thereby excluding mild forms of hemineglect that are rarely detected with current clinical tests). It could also be appropriate to recruit patients with different levels of motor weakness (from mild to severe) in order to observe whether the severity of the motor impairment modulates the perception. Witt et al. (2004) reported that throwing balls of different weights influenced perceived distance estimation. This suggests that an increase in physical effort induced a change in perception, supporting the idea that the world is perceived in function of actions and the effort associated with them. If these future studies find that a more severe hemiparesis creates a bigger lateralised perception bias, it would be an additional argument in favour of the embodiment hypothesis.

Conclusion

Conclusion

As demonstrated by the literature, hemineglect is one of the most frequent cognitive impairments after stroke, causing a major limitation for functional remission, with symptoms persisting more than one-year post-onset. This condition has been demonstrated to be heterogeneous affecting different modalities and frames of reference. Despite the extent of the impairment, a large part of fundamental research investigations and applied clinical assessment and rehabilitation has focused on visual hemineglect and overlooked links with action and action abilities.

The aim of the present thesis was to provide insights into the assessment, rehabilitation and understanding of hemineglect through perception and action measures. Firstly, we wanted to provide a sensitive measure allowing for a comprehensive assessment of visuo-spatial hemineglect and associated action kinematics. Secondly, we wanted to provide an innovative hemineglect rehabilitation using an auto-adapted serious game that combined perception and action. Finally, we wanted to enlarge the understanding of the hemineglect condition by investigating factors that modulate the perception and action link.

Throughout the thesis, we created and validated the MonAmour robot test against standardised clinical tests in stroke patients. The test demonstrated to be highly sensitive and reliable for the assessment of egocentric hemineglect and showed promising results for the allocentric component of the test. Regarding rehabilitation, we developed a sandwich shop serious game, which was demonstrated to be entertaining for stroke patients in a feasibility study. The serious game was programmed to automatically adapt difficulty through manipulations of attentional load and cue facilitation, in accordance to the patient's hemineglect severity. This allowed the game success to be controlled so that the patient would score an average of 75% success, independent of impairment severity, thereby maintaining the motivation to play the game continuously over the rehabilitation period. Across the different studies of the thesis, we deepened the understanding of hemineglect showing that patients with egocentric hemineglect demonstrated a lateralised bias towards contralesional relative to ipsilesional hemispace in omission and reaction time responses. However, no lateralization of action execution kinematics were found, suggesting that in these patients, the defect was more likely situated in the action planning than in action control processes. Results showed that the lateralised reaction time in hemineglect could be modulated by attentional load and cue types, but however not influenced by hand used or type of response required. Interestingly, the contralesional slowness was also found in patients with motor weakness without hemineglect, which could be interpreted in terms of embodiment.

Despite the methodological precautions taken throughout the thesis, several limitations have been underlined and discussed. It is therefore important to be cautious about the results and their interpretations. Future research should further investigate the various forms of hemineglect and all their potential links or implications. Furthermore, research should also focus on creating innovative, technology-driven assessment and rehabilitation, which could be combined for frequent concomitant disorders.

Taken together, this thesis was innovative by viewing the hemineglect condition under a fresh angle and investigating it with new technologies. Hopefully, the various developments and findings of this thesis will save clinicians time and help them better address hemineglect through a more wholesome understanding of the condition and its links with action. We hope that this step forward in the domain of hemineglect will broaden the minds of future researchers in this era of technological leaps, and bring some relief to the many patients whose lives, and the lives of their loved ones, are forever changed by their impairment.

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