Koji's Quest

making cognitive rehabilitation fun!

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Summary

Acquired brain injuries (ABI) are one of the leading causes of death, disability, loss of independence, and economic burden worldwide. Many people who suffer an ABI experience cognitive impairment even years after their brain injury. New solutions for cognitive treatment after ABI are needed. Nowadays, technological advances are playing an increasingly significant role in healthcare. Virtual Reality (VR) is suggested to be a feasible and useful solution that can improve both physical and cognitive deficits. Koji's Quest utilizes VR to provide a multisensory and motivating environment for rehabilitation. The software platform facilitates the ability for telehealth, which allows patients to train and assess their cognitive functions whether they are in a clinical facility or at their own home, reducing the burden placed on healthcare providers. Players will be accompanied on their quests by a virtual assistant named "Koji" and are able to play six different games that train and assess specific cognitive domains: selective attention, divided attention, visuospatial skills, memory, calculation and numerical manipulation, and executive functioning. What makes Koji's Quest unique is the fact that all games are based on the neurobiological principles of brain plasticity, observational learning (mirror-neuron system), and the brain's reward system, and that users receive both motivational feedback from their companion character "Koji," and psychoeducation regarding their training. Altogether, Koji's Quest is a promising and powerful tool for the remediation of cognitive impairment after acquired brain injury, opening new opportunities for both patients and healthcare providers.

1. Introduction

1.1. The impact of Acquired Brain injury

Acquired brain injuries (ABIs) are increasingly considered as a public burden and place a significant economic strain on society (Virani et al., 2020; Humphreys, Wood, Phillips & Macey, 2013). Among the various causes of ABI, traumatic brain injury and stroke are the leading causes of death and disability worldwide (Prabhakaran, 2012). According to the WHO, 15 million people suffer a stroke each year, together with 69 million traumatic brain injuries (Dewan et. al, 2018) this accounts for 83 million ABI cases worldwide per year. In the Netherlands, approximately 126.000 ABIs occur each year (Verheul et. al, 2016). As stroke and traumatic brain injury are not the only causes of ABI, this is an underestimation.

1.2. Cognitive problems after ABI

People who suffered an ABI commonly experience debilitating physical and cognitive impairments that are often long lasting and significantly affect their everyday functioning (Gallagher, McLeod & McMillan, 2019; Mahar & Fraser, 2011; Yip & Man, 2009). Given the functional specificity of the brain, depending upon the neuroanatomical structures impacted by an ABI, individuals can experience a variety of different cognitive problems that may be limited to one domain or multiple domains (e.g. numerical cognition, attention, memory, visuospatial, language, and executive function difficulties) (Whiteneck, Cuthbert, Corrigan & Bogner, 2016; Demeyere et al., 2015; Rehme & Grefkes, 2013; Crosbie, Lennon, Basford& McDonough, 2007). The reported prevalence of cognitive deficits after acquired brain injury (ABI) ranges from 10-
93% (van Kessel et al., 2017; Nys et al., 2007; de Haan, Nys & van Zandvoort, 2006; Nys et al., 2005; Rasquin et al., 2004; van der Naalt et al., 1999; Tatemichi et al., 1994). Cognitive deficits have a negative influence on both performance on 'activity' and 'participation' level in society (van der Kemp et al., 2017; van Velzen et al., 2009; Nys et al., 2005). As many patients are left with cognitive impairment after the first treatment for their brain injury, new and effective solutions for cognitive treatment are needed (De Luca, Calabrò & Bramanti, 2018).

1.3. Rehabilitation and VR

Research has demonstrated the importance of rehabilitation following ABI. However, despite benefits, conventional ABI rehabilitation poses several important limitations: it is time consuming, costly, labor and resource intensive, reliant upon the adherence of a patient, limited upon patient's location, and usually inadequate in frequency and intensity (Saposnik, 2016; Hung, Huang, Chen & Chu, 2016; Imam & Jarus, 2014). An increasing number of studies suggest that technological advances will play a beneficial role in rehabilitation of cognitive and motor dysfunction in individuals who have acquired a brain injury (Schiza, Matsangidou, Neokleous & Pattichis, 2019; Gamito et al., 2015; Bohil, Alicea, & Biocca, 2011). One particular technology, virtual reality (VR), has been increasingly used for the assessment and treatment of impairments resulting from ABIs due to their benefits over conventional methods (Brassel, Power, Campbell, Brunner & Togher, 2021; Saposnik & Levin, 2011). Virtual reality is defined as a computer-based technology enabling users to perform specific tasks and interact with a simulated three-dimensional (3D) environment (Saposnik, 2016; Maggio et al., 2019). Over the past ten years, research has emerged regarding the use of VR as a brain-injury rehabilitation tool, suggesting that it is a feasible and useful option that may improve physical and cognitive deficits leading to disability, while reducing costs (Laver, George, Thomas, Deutsch & Crotty, 2015; Gamito et al, 2015).

2. Koji's Quest

Koji's Quest (KQ; NeuroReality, 2020) is a Class I Medical Device intended for cognitive training and assessment, which utilizes VR to provide a multisensory and motivating environment for rehabilitation. The game allows for gaze-based play to account for brain-injury survivors who have upper-limb impairment, while neck and trunk movements remain relatively well preserved. VR controller integration can also be selected for added engagement of those who do not possess physical impairment.

There are six games aimed to train and assess specific cognitive domains by engaging players in gamified paradigms. Players are accompanied on their quests by a virtual assistant named "Koji", who is a customizable and interactive part of the game that helps to facilitate not only instruction regarding gameplay but also providing emotional support.

Gamification and the inclusion of the reward system allows for higher motivation, which increases the chances of users to repeat the training paradigms. The Koji's Quest VR software platform offers engaging daily quests and customizable sessions that can be tailored to the desired playtime. As the player progresses through each game, we have developed dynamic difficulty adjustment algorithms to ensure that individuals remain in a "flow-state", whereby the game is challenging enough to enhance the desired cognitive function and motivation to continue to play, but not so difficult that a player becomes frustrated and discontinues their training (Missura & Gärtner, 2009). Performance metrics and data regarding each cognitive domain are accessible through a user dashboard for the player or clinician to be able to track performance and compare progress between the cognitive domains.

3. The importance of telehealth

Research has shown that compared to controls who received no further treatment after being discharged, patients who continued treatment at home improved in motor function, cognitive performance and activities of daily life (ADL), 5 years after their injury (Thorsén, Holmqvist, de Pedro-Cuesta & von Koch, 2005). Remote treatment (telehealth) is emerging as an important component in healthcare systems as it has the potential to increase access to healthcare, improve health outcomes, shorten the length of stay in facilities and lessen the recourses needed for treatment. Considering the current coronavirus (COVID-19) pandemic, telemedicine is seeing a surge in popularity and use, helping to avoid unnecessary hospital visits and allowing for resources to be more efficiently utilized. With the healthcare system at its capacity, the need for technological innovations such as Koji's Quest that can offer remote care has been highlighted. Koji's Quest provides VR-based telehealth therapy that extends the reach of clinicians, so that more patients can receive the care they need.

4. Neurobiological principles and unique features

Three key principles involved in relearning cognitive and motor functions are the principles Koji's Quest is based on:

- Neuroplasticity – Research has demonstrated that the brain can rewire and reorganize following a lesion (Sebastianelli, Saltuari & Nardone, 2017; Lim & Alvarez-Buylla, 2016; Kempermann et al., 2015). Repetitive, intensive and task-oriented training is a necessary requirement for plasticity to occur (Coleman et al. 2017; Turner-Stokes, 2008; Trombly, Radomski, Trexel & Burnett-Smith, 2002; Rockwood, Joyce & Stolee, 1997). Koji's Quest allows for repetitive, intensive and task-oriented training in a safe VR-environment.

- Observational learning – Research regarding the mirror neurons system in humans remains controversial. However, research has shown that when an individual watches a task being performed, similar neural activity is produced in the brain as when performing the action themselves (Buccino, Solodkin & Small, 2006; Jang et al., 2005). When an individual has such severe impairment that they cannot actively engage in rehabilitation, it is expected that the action of observation learning alone (facilitated by watching “Koji,” the virtual assistant) can lead to favorable outcomes.

- The reward system – Research has shown that gamification of tasks and the inclusion of incremental difficulty levels can serve as a motivating factor as the player feels rewarded for their actions (Hamari, Koivisto & Sarsa, 2014; Sailer, Hence, Mandl & Klevers, 2013), increasing the likelihood of intense and repetitive training.

Furthermore, the software offers several features that contribute to cognitive rehabilitation and make training with Koji's Quest a unique experience:

- Restorative training - The restorative approach to cognitive training is based on the principle of "neural plasticity", previously discussed, which refers to the ability of the brain to adapt its structure and function as a result of training. Therefore, restorative training helps users to not only compensate for cognitive difficulties, but also restore their cognitive functioning.

- A companion character - The companion character will guide people through game-play and may serve as a buffer for technological anxiety, provide motivation via positive feedback, and improve the mood of participants.

- Psychoeducation - Koji's Quest provides information about the different cognitive paradigms that are trained within each game. In this way, users will know what brain area and which corresponding functions they are training and how this translates to activities of daily life (ADL). Additionally, a higher level of understanding may help reduce an individual's anxiety.

- Clinical dashboard – A clinical dashboard where clinicians or researchers can register users and investigate their performance is under development. Koji's Quest can capture up to 10.000 datapoints per minute. The use of technology like VR allows for more timely, accurate and unbiased measurements when compared to paper and pencil paradigms which are often subject to the administrator who observes and scores. Insights in performance data can be used to improve current training modules. We are currently working with universities and clinicians to determine the most important data to capture and display.

5. Cognitive domains targeted

As acquired brain injury patients constitute a heterogeneous population, not all individuals will experience the same cognitive problems. Based on the recommendations by the European Federation of Neurological Societies (EFNS) some of the most experienced cognitive problems following a stroke were taken into account in the game design: attention, visuospatial skills, memory, calculation and numerical manipulation, and executive functioning (Cappa et al., 2005).

- Attention - Attention is a broad concept that constitutes a prerequisite for the successful functioning of other more complex cognitive skills (Villard & Kiran, 2016) and which can be separated in different subcategories including selective attention and divided attention. Selective attention allows an individual to attend to a specific stimulus or to an object of interest, while ignoring other irrelevant information (Driver Frackowiak,

- Visuospatial skills - Visuospatial abilities allow individuals to identify visual and spatial relationships among objects and are comprised of distinct categories, such as spatial visualization, spatial perception, and mental rotation (De Bruin, Bryant, MacLean & Gonzalez, 2016). In our daily life, we need these skills, for example, to use a map to get from one point to another, to look at an object and pick it up, to drive, or to cross the road.

- Memory - Memory is the cognitive function that allows a person to code, store, and retrieve information (Zlotnik & Vansintjan, 2019). There are different types of memory, including working memory, short-term memory, and long-term memory. Working memory can be described as a temporary online maintenance of information and includes the manipulation and updating of that information (Nyberg & Eriksson, 2015; Miller, Lundqvist & Bastos, 2018). Short-term memory can only store and recall a limited amount of information for a short period of time (Cowan, 2016). Finally, long-term memory allows us to store information for long periods of time (Camina & Guell, 2017). Hamari, Koivisto & Sarsa, 2014; Sailer, Hence, Mandl & Klevers, 2013), increasing the likelihood of intense and repetitive training.

- Calculation and numerical manipulation – Calculation and numerical abilities represent an extremely complex set of cognitive processes, which require verbal and spatial memory, and executive functions (Nieder & Dehaene, 2009). We constantly use numbers in our daily file, for example, for counting items, telling the time, calculating prices, paying our bills, and solving simple equations (Nieder, 2005).

- Executive functioning - Executive functions (EF) are a set of cognitive skills that include cognitive flexibility, inhibitory control, and working memory (Miyake et al., 2000) which are essential for higher order cognitive processes such as reasoning, problem solving, and planning (Collins & Koechlin, 2012). These skills are crucial in daily life, for example, to solve an arithmetic problem, to follow a recipe while cooking, or to stop at the red light while crossing the street.

6. Transfer to activities of daily life

Cognitive deficits following ABI are linked to the poor recovery of the performance of activities of daily living (ADL) and rehabilitation outcomes (Pedersen, Jorgensen, Nakayama, Raaschou & Olsen, 1996). For example, reduced selective attention has a great influence on balance (increased risk of falling), driving (increased risk of motor vehicle accidents), and overall ADL performance. Since ABI often leads to the reduced functionality of activities of daily living (ADL), VR could offer cognitive training with a relevant and safe environment that simulates a real-life situation. In this way, VR promotes the generalization of learning strategies to real life, which conventional pen-and-paper exercises are not able to (Rizzo & Buckwalter, 1997). Research has shown the transfer of training cognitive skills to improvements in ADL. For example, Rebok et al. (2014) illustrated that older adults who participated in 10 sessions of 60-75 minutes of cognitive training for different domains showed less decrease in the ability to complete ADL than the control group, 10 years later. Another study showed that when cognitive training is combined with physical training, more improvements in ADL are seen than when physical training is offered alone (Hagovska & Nagyova, 2017).

7. Koji’s Quest games

7.1. Diamond Belt

In our selective attention game, Diamond belt, players train visual search by having to look for specific stimulus in the environment (both feature search and conjunction search are addressed) while ignoring other nontarget stimuli. This task is based on visual search tasks and the d2 Test of attention (Treisman & Gelade, 1980; Brickenkamp & Zillmer, 1998) and aims to improve selective attention, as well as information processing speed, by allowing repetitive practice and by training patients to response rapidly but selectively to information presented visually.

7.2. Alien Outpost

In our divided attention game, Alien Outpost, players train divided attention by performing two tasks at the same time. Players are asked to focus on the center spaceship and identify whether the target was present or absent, smiling or frowning, and whether the targets were equal or different. At the same time players need to locate the alien in the peripheral spaceship. The divided attention task is based on the Useful Field of View (UFOV) task (Ball, Edwards & Ross, 2007). Alien Outpost is aimed to train divided attention and processing speed by training patients to spread their attention and respond to multiple things happening at the same time.

Figure 2. Diamond Belt – selective attention

Figure 3. Alien Outpost – divided attention

7.3. Crystal Calculation

Our Crystal Calculation game consists of two phases, sequences and number manipulation. In the sequences phase, players are required to count forward or backwards in an interval. In the number manipulation phase, players are given equations to solve. The calculation tasks are based on the Serial 7s Task (Folstein et al., 1975) which is typically used as a screening procedure to assess attention and working memory functions. Chrystal Calculation is aimed to train calculation skills and working memory.

Figure 4. Crystal Calculation – calculation skills

7.4. Ancient Temple

In our visuospatial task, the Ancient Temple, players are presented with different 3D-shapes akin to Tetris blocks which should be rotated in order to fill in the gaps. The task includes two phases. The first phase is like a puzzle, where the gaps are set and presented from the start. In the second phase the gaps will appear (semi-)randomly, and players have to prevent the temple from crumbling. The game is based on Mental Rotation tasks, which require the ability to imagine rotating a 2D or 3D object (Shepard & Metzler, 1971). The Ancient Temple is aimed to train mental rotation and spatial visualization.

Figure 5. Ancient Temple – visuospatial skills

7.5. Nautilus

Our memory task takes place in an underwater world, the Nautilus. Players are asked to memorize objects and their location and recall that information after a period of time (visual long-term memory task); memorize and recall object pairs presented in clams (visual short-term memory - pairs); replicate the pattern of opening clams (visual short-term memory - sequence); and memorize the location of objects placed in the world (visual working-memory). The Nautilus is based on visual long-term recall paradigms, the Corsi Block Tapping task (Corsi, 1972) and the Digit-span task. The Nautilus is intended to train visual long-term memory, visual short-term memory and visual working memory.

7.6. Mystical Pond

The executive functioning game takes place in a sacred grove with a pond full of fish, the Mystical Pond. Fish will be jumping out of the water and the player's task is to feed them correctly. In different phases players will have to learn which food belongs to which fish, prioritize which fish to feed first, and make sure the containers are filled while feeding the fish. The executive functioning game is based on the Wisconsin Card Sorting test (WCST) and the Task Switching Paradigm (Jerzild, 1927). In the Mystical Pond, players can train different executive functions, including cognitive flexibility, decision-making, working memory and time management.

Figure 6. Nautilus – memory

Figure 7. Mystical Pond – executive functions

8. Research

During the development of our product, the opinions of a multitude of experts are evaluated and taken into account. Research is regularly conducted with scientists, doctors, other healthcare providers, patients and different types of ambassadors to make sure our product adheres to the necessary standards. In order to evaluate the effectiveness of certain implementations and the training program, a number of studies have been conducted using Koji's Quest, which will be summarized below.

8.1. Past research

8.1.1. Safety testing - January 2018-Present

The safety of Koji's Quest has been investigated with a large sample of individuals (N=89). More than 40 healthy participants have participated in the game and were assessed on negative symptoms related to the use of virtual reality as measured by the Simulator Sickness Questionnaire (SSQ; Kennedy, 1993). No significant increase in symptoms was observed, indicating that engaging in Koji's Quest is safe for use. Another 49 participants were tested for safety using qualitative interviews and user experience questionnaires addressing any adverse symptoms. No adverse effects were reported providing further evidence that Koji's Quest is safe for use. Safety testing will be ongoing during further development of Koji's Quest.

8.1.2. Reward system - January 2019-August 2019

During a pilot study examining our reward system, participants (N=18) were asked to engage in Crystalized Calculation for as long as desired, and thus played as many repetitions as they wanted. The group that played the task with our reward system implemented (experimental group, n=9), chose to repeat the game more often and thus played longer on average than those who played without the reward system implemented (control group, n=9). Semi-structured interviews also revealed that these participants experienced more feelings of reward and encouragement, and additionally felt clearer about which actions were correct and incorrect.

8.1.3. Focus groups with Hersenletsel.nl - December 2019-August 2020

Qualitative research has been conducted in order to gain feedback from individuals with brain injuries, as well as to ensure the endorsement from patient organizations. Currently several ambassadors have participated in focus groups to discuss their experience with the use of Koji's Quest. All ambassadors have responded very positively to the game and the training paradigms and signed up to stay informed of future studies.

The participants expressed that gaze-based controls felt very natural, and the participants indicated that adding controllers might make the game more challenging. VR is considered a useful tool for cognitive rehabilitation by most ambassadors, one of them quoted, "I thought Virtual Reality would make me tired, but that was not the case at all. When I sit behind a computer for 30 minutes, I'm typically very tired, but I played Koji's Quest for almost an hour without realizing it. It felt great!". The ambassadors' feedback about the product has been considered by integrating it into the design.

8.1.4. Neural activation in a 2D versus 3D environment - August 2019-January 2020

An experiment has been conducted using a neuroimaging technique called "functional near-infrared spectroscopy" (fNIRS) in order to investigate the effectiveness of Koji's Quest's selective and divided attention games by measuring frontal brain activity in a 2D computer-based versus a 3D virtual reality-based environment (N=16). The selective and divided attention games did indeed engage cortical regions associated with attention. A trend in the 2D group (n=6) was seen where selective attention was more related to ventromedial prefrontal cortex activity (the ventral "what" pathway, which mainly processes information regarding the form and identity of visual objects), whereas divided attention was more related to right dorsolateral prefrontal cortex activity (the dorsal "where" pathway, which mainly processes information regarding location). In the VR version of both game modes (n=10), the games elicited more neural activity than in the 2D condition, with the activity being more clustered in frontal regions (involved in both attention and higher-level cognitive functions such as planning and reasoning). These results suggest that VR solutions result in more brain activation compared to 2D solutions and is indicative that Koji's Quest can be used as a potential tool for inducing neuroplasticity in (post-acquired brain injury) cognitive neurorehabilitation.

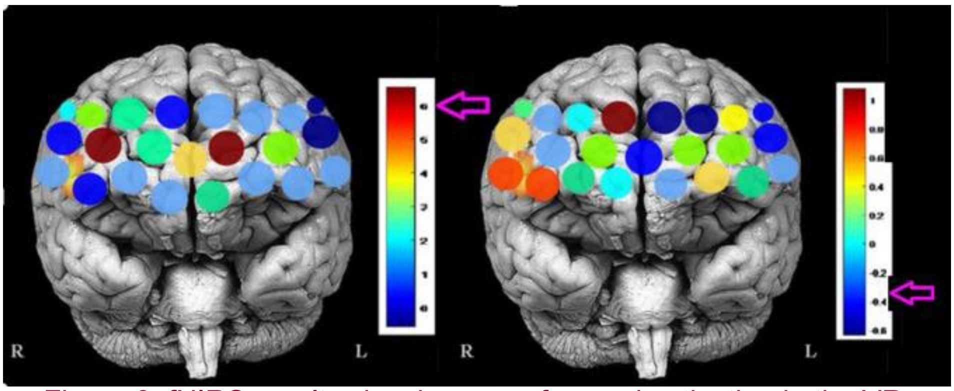

Figure 8. fNIRS results showing more focused activation in the VR condition (left) when compared to the 2D-condition (right).

__8.1.5. Koji's Quest in post-covid rehabilitation - October 2020-April 2021__

15 physiotherapists and 20 patients who were hospitalized after contracting COVID-19 were administered Koji's Quest. Patients received instructions regarding how to use the software and VR hardware, then were able to take these home to train. The recommended protocol was to play 45 minutes, 3 times per week for 6 weeks. Qualitative data on their experience was gathered. Overall, the software was found to be a useful addition to conventional rehabilitation. Despite any concerns about the costs of hardware, most participants indicated wanting to continue using VR for rehabilitation after COVID. Performance data was analyzed and each cognitive domain indicated in-game improvement. One participant quoted: “I feel in control of my rehabilitation process and it motivated me to continue” another patient said “I love playing Koji’s Quest. I feel how I’m making steps forward in improving my cognition. I keep wanting to return to this beautiful environment”.

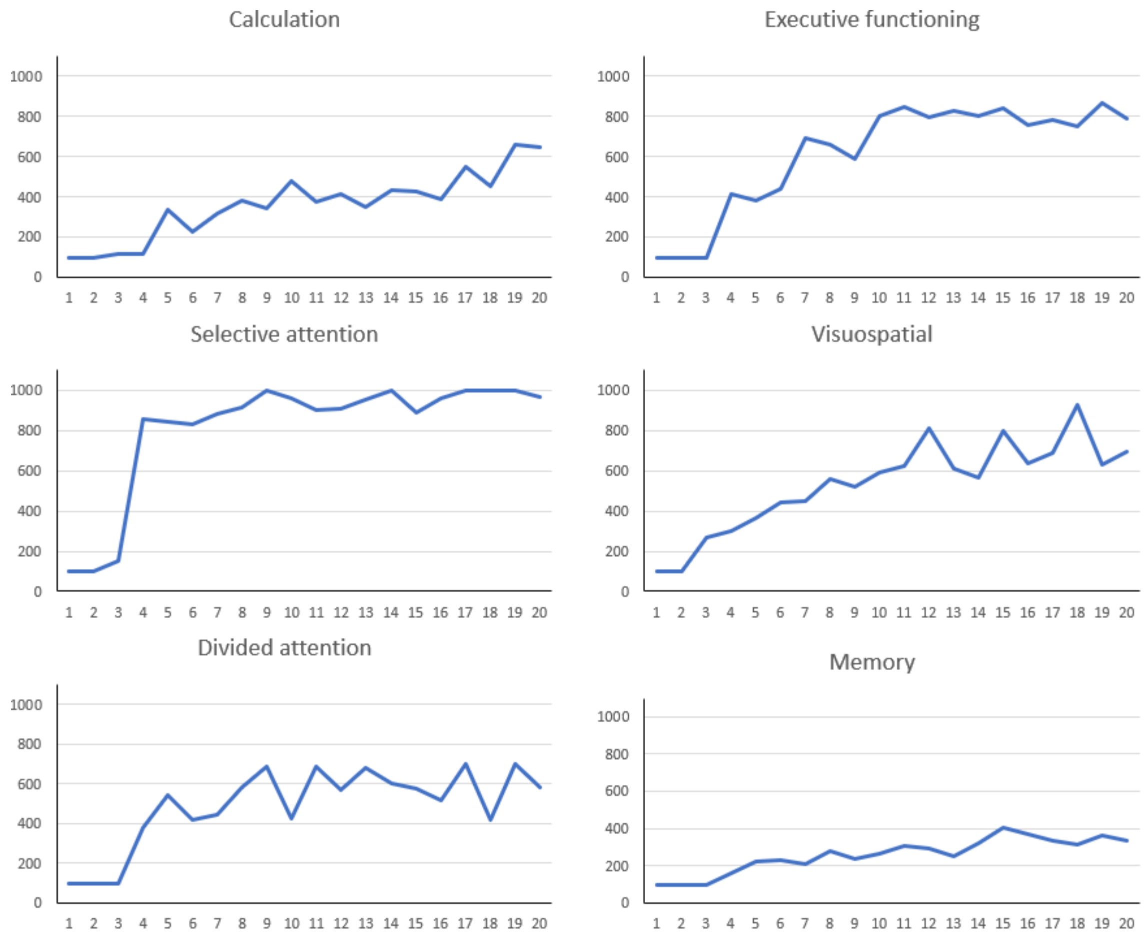

Figure 9. Average difficulty level (x-axis) per session (y-axis).

8.1.6. Pilot efficacy with Novum Zorg

Twelve long-COVID patients played Koji's Quest for 30 minutes, 2 times a week, for 6 weeks. The participants were assessed on the Montreal Cognitive Assessment (MoCA), the Stroop Color Word test and the Cognitive Failure Questionnaire (CFQ) before and after training with Koji's Quest. After six weeks of training, significant improvement on all measures was found indicating that in general, patients improved their general cognitive abilities (MoCA, p=.009), inhibition (Stroop, p=.012) and indicated subjectively that their cognition improved (CFQ, p=.002). This is an early indication that the addition of Koji's Quest to rehabilitation improves cognitive outcome measures and that patients also experience better performance subjectively.

8.2. Future research

8.2.1. Pilot efficacy of KQ treatment for ABI with Hersenletselpraktijk (Belgium)

In order to verify the efficacy of using KQ for cognitive treatment after ABI, the clinic is currently using KQ in addition to their current rehabilitation services. Preliminary results are expected in April 2022.

8.2.2. Pilot efficacy of KQ treatment for elderly with Zorggroep Solis

To investigate the feasibility and efficacy of training with KQ on cognitive functioning and activities of daily life in healthy aging elderly population, their clinic will be offering KQ as a VR-based cognitive training tool.

8.2.3. Pilot efficacy of KQ treatment in children with University of Utrecht and Wilhelmina's Children Hospital

To verify KQ efficacy for cognitive and functional treatment in children, their clinic will be offering KQ as a VR-based cognitive training tool in addition to the children's current rehabilitation. Specifically, we aim to analyse potential improvement in motivation, cognitive functioning, and activities of daily life in children with congenital heart disease and cognitive impairment. 50 children will be assessed using Koji's Quest, 12 children who display relatively low performance will be selected to follow a training program using Koji's Quest.

8.2.4. Clinical trial to validate efficacy of KQ compared to conventional rehabilitation for cognitive and functional treatment in ABI

In order to assess the validity of VR rehabilitation using KQ compared to conventional cognitive rehabilitation in improving cognition and activities of daily life, a randomized controlled study (RCT) including 300 ABI patients and 200 healthy controls will receive VR vs conventional therapy. The healthy control database will also be used for development of the algorithms AI diagnostic tool. This study will be a collaboration between NeuroReality, the University of Utrecht, Vrije Universiteit Amsterdam, Daan Theeuwes Center and Hersenletsel.nl, among others. This protocol is receiving final medical ethical approval from the UMC Utrecht.

8.2.5. To validate efficacy of KQ for cognitive treatment in Long-COVID patients in a larger sample with Radboud UMC

The 15 physiotherapists from the earlier covid-study would like to continue working with us to gain better understanding of how cognitive rehabilitation can enhance physiotherapy and increase overall health outcomes of ABI patients.

8.2.6. To validate the efficacy of KQ to improve school grades in children together with the Chichester Children's April 2022-April 2026

To verify if using KQ to train cognitive functioning has an effect in school grades, Chichester Children’s organization will be using KQ with school children in the UK. Study to begin April 25, 2022.

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