Systematic Review

Title: Mobile applications to train cognitive functions: a resource for breast cancer patients? A systematic review

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Abstract

Background
Breast cancer is an invalidating disease and, in particular, its treatment can bring serious side effects that have an impact not only in the physical aspects, but in psychological too. Specifically, cancer’s treatment could have an impact on cognitive function. In the last years, new technologies had proved to have a growing influence on health care and innovative applications can be a useful tool to deliver cognitive exercise in the patient’s home.

Objective
This systematic review gives an overview of the state-of-the-art mobile applications aimed at training cognitive functions in order to comprehend how these apps (applications) could be useful tools to counteract cognitive impairment in breast cancer patients.

Methods
We search in a systematic way all the full-text articles from the PubMed database.

Results
We included eleven studies using mobile-based application (smartphone or tablet-based) to deliver cognitive training and including a total of 819 participants. Apps’ and studies’ characteristics are presented, as well as cognitive domains trained (attention, problem solving, memory, cognitive control, executive function, visuospatial function and language). Only two apps deal with more than one cognitive domains and only three try to focus on the efficacy of the app training intervention. Apps were generally developed for a clinical population.

Conclusions
The efficacy of the training exercises are evaluated only in a few cases and cognitive domains are not well defined across studies. Another issue is that these studies are not directed to cancer patients and the applicability of the apps on this particular population should not be taken for granted. Future studies should properly test the feasibility, usability, and effectiveness of available cognitive training apps in women with breast cancer. Moreover, due to the complexity and multi-dimensionality of cognitive difficulties of this cancer population, it may be useful to design, develop and implement an ad hoc application targeting cognitive impairment in breast cancer patients.

Keywords
cognitive impairment; breast cancer; cognitive training; intervention; mobile-based interventions
Introduction

Cancer is a major public health problem worldwide; specifically, it is the second leading cause of death in the United States. In 2017, Siegel and colleagues [1] reported 1,688,780 new cases and 600,920 of estimated death. Breast cancer, in particular, is one of the most common cancers all around the world [2]. It is the most common cancer diagnosed in women, affecting in the United States about one in eight women during their lifetime (12.4%), and it is the second most common cause of death among cancer death in women [3]. The incidence rate is strictly associated with age: 95% of new cases are registered in women older than 40 years; only 1.5 cases per 100.000 are registered in young women (20-24 years). The incidence is higher for older women: 421.3 cases per 100.000 women are registered in 75-79 years old women; the median age at the diagnosis is 61 years [3]. Prognosis is related to cancer stage: 5-year survival rate is 100% for stage 0 and 1, 93% for stage II, 72% for stage III and 22% for stage IV [3]. In the last 20 years, we witnessed a decline in overall cancer mortality. This is especially true for breast cancer mortality: death rate steadily decreased of 38% from 1989 to 2014. This is due especially to reductions in smoking and advances in early detection and treatment [1].

The advances made in breast cancer treatments offer women greater prospects of cure and a better quality of life. However, on the other side, cancer treatment has some serious side effect. The side effect can be an acute or long-term and can affect women with many physical, functional, emotional, financial and social difficulties [4]. An example of a psychological side effect is presented by the meta-analysis conducted by Mithcell and colleagues [5]. The authors compared the prevalence of mood disorders in cancer survivors and their spouses (17 studies) with the incidence in healthy people (26 studies). The results showed that the prevalence of depression is higher in cancer survivors (11.6%) than in healthy control individuals (19.2%). The incidence of anxious symptomatology is even more widespread in cancer patients. Specifically, while the prevalence of anxiety is 17.9% in the patient’s group, it’s only 13.9 in the healthy control group.

Survivors women's risk and symptomatology are not just psychological. Fallowfield and colleagues [4] reported that women cured for breast cancer suffer from lymphedema, fatigue, vasomotor complaints, sexual dysfunction, and cognitive impairment as well. Moreover, literature demonstrated that cognitive impairment could be a relevant short- or long-term outcome or side effect of the treatment of several diseases, such as stroke [6], HIV and hemophilia [7], multiple sclerosis [8]. More specifically, in the recent period, a growing body of literature has focused on cognitive impairment following breast cancer's treatments in survivor women. The American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline [9] showed that the rate of patients reporting cognitive impairment during treatment is up to 75% and 35% after treatment. In addition, in the everyday clinical practice, women with breast cancer often report subjective cognitive complaints in different domains of cognition. These cognitive impairments include, for example, problems with concentration, executive function and memory [9], and, especially in patients treated with chemotherapy, problems with visual memory, information processing speed, verbal memory [10]. Cognitive impairments could also reduce the quality of life, lead to distress and have a negative impact on the role of family, workplace, and society [9].

This cognitive impairment could be determined by multi-factorial causes. Runowicz and colleagues [9] reported that insomnia, depression, fatigue, surgery, and anesthesia could be caused by cancer itself but also by different type of cancer treatments. For example, a meta-analysis conducted by Jim and colleagues[11] showed that breast cancer survivors treated with chemotherapy suffer
small and limited observed cognitive deficits. This is especially true for the two domains concerning verbal and visuospatial ability. However, other difficulties also concern memory and attention deficits due to chemotherapy. These symptoms, generally known as chemobrain or chemofog, are experienced by a lot of women cured with chemotherapy [4]. Bakoyiannis, and colleagues [12] conducted a systematic review on the impact of endocrine therapy on cognitive functions of breast cancer patients. They especially investigated difficulties in five cognitive domains: verbal memory, verbal fluency, attention and working memory, motor speed and psychomotor speed. They concluded that endocrine therapy may alter cognitive functions in these women.

The mechanism underlying cognitive impairment is still not clear. For example, empirical evidence exists on the role of stress and coping styles [13], direct neurotoxic injury, telomere shortening, oxidative stress, cytokine dysregulation, estrogen-mediated effects, genetic polymorphism [14], peripheral proinflammatory cytokines [15], decreased estrogen levels and structural brain changes [16] in cognitive impairment following cancer treatment. There are still some uncertainties regarding the nature and the magnitude of cognitive impairment in breast cancer patients [17] and also regarding the most effective treatment to target this kind of cognitive difficulties [9]. In their review on pharmacological and non-pharmacological interventions to manage cognitive alterations after chemotherapy, Chan and colleagues concluded [18] that pharmacological interventions to manage cognitive alterations after chemotherapy for breast cancer are not well supported by evidence. Instead, some kind of cognitive training - like computerized cognitive training, cognitive behavioral therapy, memory training, speed of processing training, psychoeducation, Tibetan sound - and physical interventions may be useful. However, further studies are needed in order to provide guidelines and concrete recommendations for clinical practice [18].

Overall, these psychological interventions for cognitive impairment are generally money consuming and may result in a huge burden for patients because they are often delivered in an in-patient context. [17]. The development and delivery of home-based or web-based interventions may be several advantages over traditional clinic-based ones. However, now, there is a scarcity of this kind of innovative interventions for cognitive training.

About 25 years ago, Tim Berners-Lee creates the "World Wide Web". Internet nowadays has become essential. The "Digital in 2017 Global Overview" state that currently, more than half of the world's population is connected to the internet and uses a smartphone. A common misunderstanding is that older adults are not interested in technology to compare to younger people. As reported by the Pew Internet and America Life Project, older people are rapidly gaining more interest on the subject. For example, Pew survey shows that the rate of people aged 65+ using internet grew from 14% in 2000 to 66% in 2018. Internet usage for other groups of age is growing as well. The internet usage increased from 70% in 2000 to 98% in 2018 for people aged 18-29, from 61% to 97% for people aged 30-49, and from 46% to 87% for people aged 50-64. These statistics are especially interesting because it could be the promise of the development of innovative web-based interventions. Traditional healthcare interventions have been delivered through a face-to-face meeting with clinicians: However, has increasingly spread in the last decades[19].

The two leading platforms for health-related applications are the IOS and Android. In 2014, more than 100.000 mHealth apps (applications) have been released [20] [21]. mHealth and mobile health apps permit a real-time and bidirectional interaction with the patient [21]. This transformation brings changes even in the diagnosis and treatment of cancer.
Several mobile health apps and mHealth system have been developed to inform patients, enhance communication and consulting, symptom self-management and monitoring, improve health record access and maintenance, and clinical decision making [22]. However, little is known about mobile applications directly aimed at improving cognitive functioning in patients reporting cognitive difficulties. Given the importance of identifying effective training interventions to counteract cognitive impairment in breast cancer women, we conducted a systematic review aimed at identifying developed mobile applications for the training of cognitive functions in both clinical and non-clinical populations. We focused on the mobile applications’ characteristics, populations and cognitive domains trained to identify which mobile applications have been developed and to evaluate their usefulness, efficacy, and suitability for breast cancer women reporting cognitive impairment.

Methods

Our search strategy was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) [23]. Flow chart of the systematic review is shown in Figure 1.

To identify articles for our review, we searched the PubMed database for a combination of the terms smartphone, mobile and app. The searched cognitive domain was: memory, attention, concentration, verbal fluency, motor speed, psychomotor speed, problem-solving, executive function, visuospatial function, language and cognitive control.

In particular, the string of terms was: ((((smartphone) OR mobile)) AND app) AND ((((((((((cognitive) OR memory) OR attention) OR concentration) OR verbal fluency) OR motor speed) OR psychomotor speed) OR problem solving) OR Executive function) OR Visuospatial Function) OR Language) OR cognitive control). The search was limited to English language and full text. No restriction was placed on the year of publication. The search was completed in February 2018.

GM and LV reviewed the titles and abstracts from PubMed to identify relevant papers. We extracted only those papers with the main focus on the use of the mobile-based application (smartphone or tablet-based) to deliver cognitive training. About ten percent of all papers were double screened and disagreements in data extraction were resolved through discussion.

Then, the second step consisted of a full article screening. We excluded papers that are: 1) review, case report or protocol; 2) not full-text articles; 3) related to mobile applications that assess cognitive functions without training them.

Data collection included information on: authors, title, publication date, study type, study aim, sample characteristics, clinical or non-clinical populations, cognitive domains trained, apps’ exercise description, assessment and feedback, apps’ evaluation and efficacy, training with the experimenters, and whether the device was given to the study participants.
Figure 1: Study selection process

- Records identified through database searching (n = 446)
- Records after duplicates removed (n = 446)
- Records screened (n = 446)
  - Records excluded (n = 399)
  - Full-text articles assessed for eligibility (n = 47)
    - Full-text articles excluded, with reasons (n = 36):
      - Reviews (n = 2)
      - Case reports (n = 5)
      - Subject (n = 16)
      - Cognitive assessment (n = 11)
      - Protocols (n = 2)
- Studies included in qualitative synthesis (n = 11)
Results

Studies selected
Flowchart of the systematic review is shown in figure 1. We retrieved a total of forty-seven articles. We selected eleven articles after a full-text screening. We excluded a total of two reviews [19,35], five case reports [36–40] and two protocols [41,42]. Sixteen studies were excluded from the present systematic review because they did not use mobile applications to train cognitive functions [20,43,52–56,44–51]. Eleven studies were exclude because they used mobile applications only to assess – and not to train - cognitive functions [57,58,67,59–66]. Our selected studies focus on the cognitive domains of attention, memory, problem solving, cognitive control, executive function, visuospatial function, and language (as reported in Table 1).

Table 1: app’s developer, names and cognitive domains being targeted in each study

<table>
<thead>
<tr>
<th>Author, year</th>
<th>App’s name</th>
<th>Attention</th>
<th>Problem Solving</th>
<th>Memory</th>
<th>Cognitive Control</th>
<th>Executive Function</th>
<th>Visuospatial Function</th>
<th>Language</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blackburne, 2016 [25]</td>
<td>NoGo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bless, 2014 [26]</td>
<td>-</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hill, 2015, and Hill, 2017 [27] [28]</td>
<td>Attention Training Application</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorusso, 2017 [29]</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lu, 2017 [30]</td>
<td>Brain Win</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Powell, 2017 [31]</td>
<td>ProSolv</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacchino, 2015 [33]</td>
<td>Cognitive Training Kit (COGNITRACK)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Zmily, 2014 [34]</td>
<td>AD cope - Spaced Retrieval Exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Characteristics of the ten included studies and of the relative apps are presented in Table 2 and Table 3. Each study and each app will be introduced and described in detail in the next section.
Table 2: summary of studies' characteristics in term of study type, aim and sample
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Type</th>
<th>Aim</th>
<th>Sample</th>
<th>N</th>
<th>Age</th>
<th>Country</th>
<th>Population Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arean, 2016 [24]</td>
<td>Randomized Controlled Trial</td>
<td>To test outcome and clinical patterns of three different mobile apps for depression</td>
<td></td>
<td>626</td>
<td>Mean: 33.9 SD: 11.8 Range: -</td>
<td>USA</td>
<td>Adults with mild to moderate depression</td>
</tr>
<tr>
<td>Blackburne, 2016 [25]</td>
<td>Randomized Controlled Trial</td>
<td>To examine the efficacy of a training programme for inhibitory control</td>
<td></td>
<td>52</td>
<td>Mean: 35.2 SD: 14.1 Range: 19-61</td>
<td>Australia</td>
<td>overweight or obese adult. - training participant, -waitlist/control</td>
</tr>
<tr>
<td>Bless, 2014 [26]</td>
<td>Randomized Controlled Trial</td>
<td>To test the feasibility of an app for training attention</td>
<td></td>
<td>28</td>
<td>Mean: 23.3 e 23.9 Range: -</td>
<td>Norway</td>
<td>Healthy individuals -non-training control group -training control group</td>
</tr>
<tr>
<td>Hill, 2015 [27]</td>
<td>Pilot study</td>
<td>To test the app feasibility</td>
<td></td>
<td>9</td>
<td>Mean: 76.1 SD: 5.5 Range: 64-96</td>
<td>USA</td>
<td>Old Adults</td>
</tr>
<tr>
<td>Hill, 2017 [28]</td>
<td>Descriptive Study Design</td>
<td>to evaluate the usability and acceptability of an app to train attention</td>
<td></td>
<td>12</td>
<td>Mean: 79 SD: 4.2 Range: -</td>
<td>USA</td>
<td>Old adults</td>
</tr>
<tr>
<td>Lorusso, 2017 [29]</td>
<td>Observational</td>
<td>to evaluate learnability, usability, user satisfaction and quality of the interaction between an app to train language and children</td>
<td></td>
<td>14</td>
<td>Mean: 60.1 Month SD: 6.2 Range: 50-68 month</td>
<td>Italy</td>
<td>Children with mild to severe language impairments or delays</td>
</tr>
<tr>
<td>Lu, 2017 [30]</td>
<td></td>
<td>to develop an improved design for game-based cognitive training for seniors using mobile devices.</td>
<td></td>
<td>9</td>
<td>Mean = 82.7 2Mean = 69.6 SD1 = 7.2 SD2 = 9.4 1= 4 e 2= 5 Range1: 73-90 Range2: 61-84</td>
<td>Taiwan</td>
<td>Old Adults</td>
</tr>
<tr>
<td>Powell, 2017 [31]</td>
<td>Randomized Controlled Trial</td>
<td>To develop and test an app to train problem-solving in everyday life for patients following brain injury.</td>
<td></td>
<td>23</td>
<td>Mean: 44 SD: 15 Range: 20-75</td>
<td>USA</td>
<td>Brain injuries adults. -Control group. -Intervention group</td>
</tr>
<tr>
<td>Shellington, 2017 [32]</td>
<td></td>
<td>to explore the feasibility and utility an app to deliver physical exercise outside the laboratory</td>
<td></td>
<td>20</td>
<td>Mean: 68 SD: 5.4 Range: 59-76</td>
<td>Canada</td>
<td>Older adults with and without Subjective Cognitive Complaints (SCC) and Mild Cognitive Impairment (MCI)</td>
</tr>
<tr>
<td>Tacchino, 2015 [33]</td>
<td></td>
<td>to describe the design of an app based on intensive cognitive rehabilitation based on working memory exercise and to test its usability for patients with multiple sclerosis.</td>
<td></td>
<td>16</td>
<td>Mean: 49.1 SD: 9.1 Range: 33-67</td>
<td>Italy</td>
<td>Cognitively impaired patients with multiple sclerosis</td>
</tr>
<tr>
<td>Zmily, 2014 [34]</td>
<td>Observational</td>
<td>to develop an improved design for game-based cognitive training for seniors using mobile devices.</td>
<td></td>
<td>10</td>
<td>Mean: 68 SD: 5.4 Range: 59-76</td>
<td>Jordan</td>
<td>Patients with multiple sclerosis</td>
</tr>
</tbody>
</table>

*Note: The data provided is a representation of the table content and may not be completely accurate due to limitations in the extracted text.*
Table 3: summary of main aspects of apps and their evaluation
<table>
<thead>
<tr>
<th>Authors</th>
<th>Domain Trained</th>
<th>Exercise Description</th>
<th>Assessment And Feedback</th>
<th>Evaluation</th>
<th>Training With Experimenter</th>
<th>Device Given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arean, 2016 [24]</td>
<td>Cognitive Control</td>
<td>Created as a videogame</td>
<td>Half individuals downloaded the app. App used 10.78 times</td>
<td>Not evaluated</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Blackburne, 2016 [25]</td>
<td>Inhibitory Control (Cognitive Control)</td>
<td>3 components of inhibitory control: - unhealthy eating, - smoking, - alcohol consumption. Training task is based on “Go/NoGo and stop signal task”</td>
<td>X</td>
<td>Not evaluated</td>
<td>Improved inhibitory control in training group</td>
<td>X</td>
</tr>
<tr>
<td>Bless, 2014 [26]</td>
<td>Auditory Attention</td>
<td>Training task is based on the “forced-attention conditions of the consonant-vowel dichotic listening paradigm”</td>
<td>Not evaluated</td>
<td>Better performance and lower activation in brain in the training group</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Hill, 2015 [27]</td>
<td>Attention</td>
<td>The training task is based on three parts: presentation of visual stimuli alone, presentation of auditory stimuli alone, a combination of visual and auditory stimuli</td>
<td>Low feasibility</td>
<td>-</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Hill, 2017 [28]</td>
<td>Attention</td>
<td>The training task is based on three parts: presentation of visual stimuli alone, presentation of auditory stimuli alone, a combination of visual and auditory stimuli</td>
<td>Positive usability, interest, enjoyment, and satisfaction. Difficult to use the app alone</td>
<td>Not evaluated</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Lorusso, 2017 [29]</td>
<td>Language</td>
<td>Training task is based on activities to improve lexical-semantic knowledge and skills.</td>
<td>Easy to understand and learn, engaging and rewarding.</td>
<td>Not evaluated</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Lu, 2017 [30]</td>
<td>Attention - Executive Function -</td>
<td>Training task is based on four types of</td>
<td>Acceptable and satisfying not evaluated</td>
<td>X</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
Sample characteristics

Our search comprehends 11 studies that analyzed a total of 819 participants. The number of participants in these studies ranged from 9 to 626. Weighted by sample size, the mean age of participants was 36.2 years old. However, there is a huge heterogeneity in participants’ age among these eleven studies. Indeed, age ranges from a minimum of 50 months to a maximum of 96 years. In particular, a study focused on pre-school children with a mean age of 60 months [29], while four papers focused especially on older adults with a mean age over 68 years [27,28,30,32].

Nearly all the studies were performed in developed countries. Almost half of the eleven studies (5) were conducted in North America, four of them were performed in the United States of America [24,27,28,31] and one in Canada [32]. Three were conducted in Europe: two in Italy [29,33] and one in Norway [26]. Two Asian studies were conducted in Taiwan [30] and in Jordan [34]. Only one study was conducted in Oceania and specifically in Australia [25]. In addition to this heterogeneity in cultural provenance, the eleven identified studies have also a moderate variability in the kind of population in which they evaluated the app for the cognitive training. Specifically, ten out of eleven studies involved adults or elderly people. One study focused on adults affected by brain injuries [31], another one on cognitively impaired patients with multiple sclerosis [33] and the third study on patients with early stages of Alzheimer Disease [34]. Three papers focused on healthy older adults [27,28,30] while one study chooses a population of older adults with and without Subjective Cognitive Complaints and Mild Cognitive Impairment [32]. One study focused on adults with mild to moderate depression [24], one on overweight or obese adult [25]. Just one paper from our search specified on healthy adults [26]. Only one study focused on children with mild to severe...
language impairments or delays [29]. Inclusion and exclusion criteria were very different in all the studies. Only three studies [25,26,31] included the presence of control groups.

Aim
The majority of the selected papers had a primary aim to evaluate the apps’ in terms of usability, acceptability, feasibility and user satisfaction [26–29,32–34]. Only two articles [30,31] chose to describe the development and the improved design of the apps. Only one paper [24] had as the main aim to assess and improve depressive symptoms by comparing three different apps, one of which is explicitly aimed at improving depression through a cognitive control exercise. Just one study had the explicit aim of investigating the efficacy of the app in improving cognitive functioning [25].

App characteristics
Apps’ availability in the market was checked by searching them in the main app stores (IOS and Android): however, none of them is already available to the general public. The same search was conducted on online test catalogs, such as Pearson Assessments or Psychological Assessment Resources, Inc. (PAR, Lutz, FL, USA). Even in this case, the apps were not already available to the public. In all the identified studies, app users were asked to respond with a touchscreen. A brief description of the functioning of each app is now introduced.

Bless and colleagues [26] explored the feasibility and the effectiveness of a mobile application that enable people to train auditory attention. They directly developed this in-house app, but they did not give it a name. Participating in this study were healthy adults; they were given an iPod touch and asked to perform a CV-DL task. According to the forced-attention condition of the standard CV-DL paradigm, during this task, each participant was presented simultaneously with two different syllables via earphones: while one was presented to the left ear, the other was delivered to the right. Syllables, made by consonants and vowels, were read by a male, native Norwegian speaker with constant voice intonation and intensity. Before the beginning of the task, each participant was told by a message on the display to pay attention only to the syllable delivered to the left or the right ear. After hearing the syllables, he/she had to choose the correct syllable between six multiple choice answers. Every training session, about 6 minutes long, was made by six blocks with five pairs of syllables. Syllables were presented in 400-500 ms with an interval of 4000 ms between each pair. At the end of every session, participants were shown a feedback of their correct answers. Results were stored on the device and available to the researcher at the end of the study.

Lorusso et al. [29] developed an application to improve semantic competence and structural knowledge in children with learning impairments. It was part of an integrated system. The aim of the study was to evaluate learnability, usability, user satisfaction and the quality of the interaction in children playing with this integrated system. The app was used on a supplied tablet; it scanned the tag that the experimenter had placed under some toys (plastic animals). When the children scanned the tag under the toys, the app displayed a menu with five different activities that were all related to this specific animal. The first was an informative activity in which children were given some interesting information about this specific animal. The second one was a storytelling activity that directly connected to a website with stories and tales related to the animal. The third was a visual activity with several picture and photos of this specific animal. The fourth one presented a song strictly related to the chosen animal. The last one was a puzzle activity in which children were asked to put together pieces of a puzzle representing this specific animal. The authors chose all these activities because they enable enrich semantic knowledge and organization. After the
completion of each the task, each child was given a picture or a sound feedback. The app provided also a text-to-speech tool to listen to written information.

Shellington and colleagues [32] examined the feasibility and utility of an app called HealtheBrain. The app was focused on improving visuospatial executive function and working memory. Participants of this study were older adults, either with or without subjective cognitive complaints and mild cognitive impairment. They received HealtheBrain to improve cognitive functioning through a specific physical exercise called Square Step Exercise. Before the beginning of the exercise the app offered participants the opportunity to have a tutorial about the use of the app and then to calibrate the step length. The square step exercise had 35 progressive stages and the participants had to start to form the first one. In order to go from one level to another, the subject had to complete at least 80% of each task. For each step, participants had to memorize 4-8 walking and stepping sequences and repeat them. When they reached the goal, an item was added to their virtual garden and they could get to the next level. While they were asked to exercise (2-3 time a week, at least 3 times a week), subjects were invited to contact the researchers for every question or technical issue.

dual n-back training targets the cognitive domain of attention
dual n-back training targets the cognitive domain
In 2015, Hill and colleagues’s [27] developed an application to train attention. More recently, they [28] decided to improve it considering the problematic issues identified in their previous study of. Both studies focused on the usability, acceptability, and feasibility of the Attention Training Application. The experimental design of the study of 2017 was very similar to the one of the pilot study of 2015. Before the start of exercise two preliminary sessions were established: in the first session an examiner met with a participant in order to introduce them to the device (iPad or iPad Mini). Prior to the beginning of the trial, the participants could exercise on using the device for a whole week to become more familiar with its functioning. The app was then introduced in the second session. The written instruction was given to participants and they were able to contact the experimenter to receive further information and instructions on the use of the app and device. This app delivered an attention training program targeting attention and based on the dual n-back training paradigm. This cognitive domain was improved by different exercise: for the first one a visual stimulus was presented, for the second one an auditory stimulus was given and finally, for the third step a visual and an auditory stimulus were presented together. The visual stimulus was a grid split in eight parts with a square in one of them. The auditory stimuli were spoken letters. Given that the authors follow the n back paradigm, the exercise requested that the subjects had to answer as the exercise presented before the last. At the end of each trial, the app sends a visual stimulus so that the participants know immediately if the answer is the correct one. The Attention Training Application was adaptive: If participants performed well, the exercise increased in difficulty. The differences between the two versions of the app used respectively in the 2015’s study and in 2017’s one, consisted mostly in modified elements to help the user to better comprehend how to use the app and to correctly perform the exercise. In 2017, authors added some preliminary training features as well, namely the first session with the experimenter that presented the iPad and the week to become familiar with the device. Moreover, feedbacks were modified from the first to the second version. Specifically, the 2015 app gave also a negative feedback to users, namely a red X indicated each wrong answer. However, this kind of feedback was removed in 2017 because participants generally reported frustration and confusion with it. Finally, the response time changed from three seconds to five seconds. The paradigm followed, and the exercise remained the same as well as the adaptive style of exercise presentation.

Lu and colleagues’ study [30] developed a prototype of an application called Brain Win. The app was directed to older people and it used two cycles of design and evaluation. The app involved four tasks and six games to train five cognitive domains: attention, executive function, memory, language, visuospatial function. The six implemented games were directly related to real life experience and daily activities of older adults. They were 1) “My calendar” referring to discrimination task and allowing to train attention, executive function and memory. Specifically, participants had to identify the correct date and time rotating the calendar proposed; 2) “Go to market” was a visuomotor task that allowed training attention, executive function, memory and visuospatial function. Participants had to draw the route to a market ace; 3) “Shopping in the market” referred to calculation task and allowed to train attention, executive function and memory. Participants were asked to buy some items with a limited budget and to make calculations with the item prices; 4) “Finding object during a phone call” was a discrimination task that allows training attention, memory, language and executive function. Participants had to listen and find correct items on the screen; 5) “Super singer” referred to respelling task and allowed to
train attention, memory, language, visuospatial function, and executive function. The participant was asked to reorganize character cards with song lyrics, listening to or reading them; 6) "Go to the zoo" was a discrimination task that allowed training attention, memory and executive function. Participants had to recognize and remember the noise made by the zoo animals and identify them. Each game was supported by visual and auditory instructions. Buttons and icons had realistic appearance and participants were asked to test the application in their home. Feedback sounds were presented at the end of each task. There was also the possibility to check the game scores or participant’s position in a ranking table.

Arean and colleagues [24] study aimed at testing the efficacy of three apps in relieving from depressive symptomatology. These three apps were called Project: EVO, iPST and Health Tips. In our review, we are mainly interested in Project: EVO. The app, in fact, trained cognitive control in order to improve cognitive symptoms. The other two apps, instead, were used to control treatment (Health Tips) and to conduct psychotherapy intervention to improve depression (iPST). The participant had to use just one of the three apps: if they own a smartphone but not an iPad the experimenter gave one of them to participants. Project: EVO is an exercise to train cognitive control and is designed as a video game. As the participants improved their proficiency with the game over time, the app intensified the difficulty of the presented exercises. The app had an internal system to remind the individuals to complete the exercise.

Blackbourne and colleagues [25] tested the efficacy of the NoGo app that considered cognitive restraint - and specifically inhibitory control - to be used for weight control in obese adults. In particular, the app trained three domains: unhealthy eating, smoking and alcohol consumption. Each game had two distinct tasks: 1) Go and Nogo trials, in which a timer appeared next to an image - that remained the same- and started to countdown; 2) Stop trial, in which participants had to choose the healthy food image as fast as possible. In this exercise, the image changed from healthy to unhealthy after the countdown start. Participants had to tag the correct answer if the "Go" tone was produced, instead, if the tone of "Nogo" was reproduced, participants had to hold back from answering. The stimuli presented a change in each game so that the individuals could not anticipate and predict the next image and could not respond based on their previous experience with the game. The difficulty level was modulated by the timer and by the number of images presented (there is a maximum of 12 images). The app permitted to collect data such as reaction time, game level, correct responses, and errors. The researcher could gain access to the data at the end of the training session.

Powell and colleagues [31] aimed at developing and testing an app called ProSolv. It was a problem-solving-based application developed by authors through focus group and interviews. In this study, the device was not given by the examiner; in fact, one of the inclusion criteria of the study was that each participant must be an owner of a smartphone with a working internet connection. The ProSolve programme comprehended three steps. The first was a face-to-face meeting with a coach; during this session, each participant could understand and test the app with the help of the expert and the programme's manual. In a second, a web-based tutorial introduced the conceptual model of problem-solving and its usefulness in everyday activities. Next, the use of the app is explained in a video. The third and final step consisted of directly using the ProSolv application. The app helped participants in creating a problem-solution list and in remembering each step to solve problems in a more effective way. The app was composed of four pages: the "Welcome to the ProSolve app", the "My problem", the "My solution" and the "My contact". With the app, individuals could evaluate each problem-solution of the list by rating them with a 5-star
The last features of the ProSolve application was a FAQ or help page in which each participant could find further information about the app.

Tacchino and colleagues [33] described the Cognitive Training Kit (COGNI-TRAcK). In their study, the app was used for a cognitive rehabilitation intervention based on working memory exercise in a sample of patients with multiple sclerosis. The authors stated that COGNI-TRAcK could be used to implement three types of working memory. The first task targeted Visuospatial Working Memory and presents a sequence of visual stimuli, one at time. At the end of stimuli’s presentation, each participant was asked to touch the corresponding location of the stimuli on the screen. The second task was an Operation N-back exercise in which participants were presented with two numbers on the screen. If the instruction on the screen said N=0, participants had to touch the sum of the two number as the right answer. When the instruction said, for example, N=1 they had to touch on the screen the sum of the numbers previously presented. The third is Dual N-back exercise in which each patient was presented with single a number on the screen. Similarly, to the N-back task, if the instruction said, for example, N=1, participants had to remember and recall the number presented in the previous exercise by touching it on the screen. All the information gathered with the app were directly stored in a database. The database was composed of three sections: “patients” that contained participant’ data; “exercise and treatment” that contained information about the assignment, the workload, the record of the exercise and length of the intervention, and a third section of the database that contained the characteristics of the configuration of the app and was called “setting”. The main feature of the app was the possibility to implement the workload and regulate its intensiveness.

Zmily and colleagues’ study [34] focused on the usability of sub-task of an integrated application named ADcope. The app was developed for mobile devices and aimed to support Alzheimer disease patients in their daily routines. During the study, all the patients were given a tablet with the application along with clear instructions on how to use device and app. Patients were asked to perform exercises while sitting together in a room. The application was made up of three parts. The first one aimed at improving the users’ quality of life. The second part was a support module. For our review, we focus specifically on the third part that aimed to exercise patient’s memory. The authors integrated two exercises in this part: 1) Audio Assisted Memory Training that played audio files of each patient’s biographical information and then quizzed him/her about that; 2) The Spaced Retrieval Exercise whose usability was the main focus of this Zmily and colleagues study. This specific exercise was made in two phases: the first one assessed users’ current memory recall ability by presenting them information followed, after some delay, by a question with a four-multiple choice answer. This exercise could use text information or a simple figure. The difficulty of the exercise could be operationalized by measuring the length of the delay between the information and the quiz. If the individual gave the right answer after a certain period of time, the app would increase the difficulty by increasing the time delay. The training phase (the same as the assessment) was made by ten questions which have a delay length based on the assessment results. After completing the trials, a written feedback appeared on the display. The app provides also text-to-speech tools that enable each patient to be presented with a read aloud information.

**Cognitive domains**

As shown in table 1, the cognitive domains trained by the identified apps are: attention, problem solving, memory, cognitive control, executive function, visuospatial function and language. Eight
out of ten studies considered the usefulness of the app for the training of just one cognitive domain at a time (cognitive control [24,25], attention [26,28], language [29], problem solving [31], memory [33,34]). Instead, two studies considered more than one cognitive function: Lu and colleagues [30] investigated attention, memory, executive function, visuospatial function and language; Shellington and colleagues [32] investigated memory, executive function and visuospatial function.

**Cognitive control**

Cognitive control was trained in two different studies: Arean and colleagues [24] and Blackbourne and colleagues [25]. Both of these authors stated that the app usage could improve cognitive control as a mean to enhance other conditions: depression for Arean and obesity for Blackbourne. Cognitive control in Arean’s paper was trained with an app that is designed as a video game that modulates cognitive control abilities. Blackbourne instead reported the efficacy of cognitive control training in food consumption in an obese population.

**Problem solving**

People with cognitive impairment following brain injury often lack problem-solving skills and a web-based approach could be useful in rehabilitation [31]. The ProSolv app for Powell and colleagues could be a useful tool to help solve this issue. The deficit in problem-solving was trained through the creation of a personalized problem-solution list and with the possibility to use the app as a resource for remembering the step to effective problem-solving.

**Memory**

Memory was considered by Shellington and colleagues [32], Tacchino [33], Zmily [34] and Lu [30]. This cognitive dimension was analysed in different samples and with different meanings in all the authors. Tacchino and colleagues and Zmily and colleagues explored how to train memory in serious disease that causes cognitive impairments: multiple sclerosis for Tacchino and colleagues and Alzheimer’s disease for Zmily al. Lu et al.’s and Shellington and colleagues’ studies had the same interest: investigating memory impairment in an older population. As they referred to a different kind of population, the authors explored different kind of memory. Tacchino and colleagues referred to working memory. Working memory training can lead to changes in healthy individual's brain structures and can improve cognitive function, useful in the daily life. The improvement is demonstrated in cognitive impaired patients as well. Tacchino and colleagues’ study focused on multiple sclerosis as it is a cognitive disabling condition and it affects all age patients. Another disease that has serious effects on cognitive impairment is Alzheimer’s disease. Memory impairment in Alzheimer’s disease was the focus of Zmily and colleagues’ work. In particular, it considered the recall ability. Recall abilities was trained to help individuals to retain critical information longer and consequentially improve their quality of life.

Lu and colleagues and Shellington and colleagues worked with a sample of old adults. Shellington and colleagues considered old adults with and without subjective cognitive complaints and mild cognitive impairment. In the study, the authors tried to train memory with physical activities. They stated that physical exercise was associated with the higher cognitive function; they improved it with Square Stepping Exercise that was proved to train memory skills. Lu and colleagues, instead, had a healthy old adult’s sample. In their study, age-related memory decline had an effect on recollection ability during information finding and retrieval. Memory was trained with four tasks: discrimination, visuomotor, respelling and calculation.

**Executive function**
Lu and colleagues (Lu and colleagues, 2017) reported some evidence on age-related decline in executive function and performance, these abilities are generally affected by the decreases of the working memory functioning and by the perception of time. Deficiency in this domain is related to future functional impairment. Neurochemical, localized and process aging theory indicate that age-related cognitive changes affect also executive functioning. Brain Win, the mobile application developed by authors, stimulated also executive function in all the game contexts, with four different type of task (discrimination, visuomotor, respelling and calculation). Shellington and colleagues [32] in their paper, instead, considered executive function related to physical exercise. They considered physical activities as a mean to train executive function. Their app, Health e Brain suggested a series of exercise, called Square Step Exercise, in order to implement the cognitive domain.

**Visuospatial function**

"Brain Win", the application developed by Lu and colleagues [30], stimulated the visuospatial function with two different task. The first is a visuomotor task named "Go to the market", the other is the "Supersinger". "Brain Win" was specifically developed to improve visuomotor ability in older adults in which visuospatial function is affected by age-related cognitive changes, including visuospatial attention, memory and orientation decline. The visuospatial function is the focus of Shellington and colleagues’ [32] work as well. Their study combined physical activities with cognitive training. In particular, they focused on a series of activities called Square Step Exercise. This exercise could be described as a visuospatial working memory with a cued stepping response also known as mind-motor exercise.

**Attention**

Four studies considered the cognitive domain of attention [26–28,30]. In particular, Bless and colleagues focused on a mobile application to train the auditory attention, based on the forced-attention conditions of the consonant-vowel dichotic listening paradigm. Individuals have to listen to two auditory stimuli simultaneously in two different ears while paying attention to only one of them. According to the authors, this paradigm could be considered as an analog task to some everyday life situations in which people are asked to effectively master different and confounding auditory events. The authors reported that some deficits in auditory attention could be found also in clinical conditions like schizophrenia, pre-term born adolescents, dyslexia as well as aging. In their study, the authors tried also to see if the trained task has transfer effects on cognitive interference and attentional task in daily visual and auditory domain activities. Hill and colleagues’ [27,28] Attention Training Application is based on dual n-back training paradigm and targets attention in elderly people. The authors reported that through aging, some attention's aspects could tend to decline, for example, with increasing age, the ability to divide or switch attention could shiftily decline. Attention is a cognitive function that has a pervasive influence on several daily activities. Thus, its training may also lead to improvements in other cognitive performance aspects and enhance the appropriateness of several daily life activities. Specifically, the authors highlighted that the effect of the dual n-back task could be transferred also to other cognitive abilities.

Also, Brain Win application, developed in a working prototype for older adults by Lu and colleagues [30] targets the cognitive domain of attention. This app directly stimulates attention with four different types of game, such discrimination, visuomotor, respelling and calculation task.

**Language**
Two studies directly focused on training the cognitive domain of language [29,30]. Lu and colleagues started from reporting evidence of a decline of the language functioning in elderly people. Specifically, neurochemical, localized and process aging theory demonstrate age-related cognitive changes affecting language. Language is connected with various cognitive aspects; the decline in this domain could also affect sentence understanding and text recalling. In Brain Win, the app developed by the authors, language is stimulated through two different context games (“Finding object during a phone call” and “Super singer”) that were respectively connected to two types of abilities, namely discrimination and respelling. Lorusso and colleagues [29] focused on improving language ability either children with language impairment and typically developing children. Their system aimed to improve semantic competence and structural knowledge with various activities. The system is made up as an integrated combination of a tablet, a group of plastic toys, the Near Field Communication technology and a custom app that allows children to play with various activities to train specific cognitive processes and abilities, such as mental representation, conceptual networks, semantic versus structural world knowledge. All these aspects are especially relevant in speech and language development and functioning.

**Efficacy**

Only three out of ten studies directly evaluate the app’s in improving cognitive abilities [25,26,31]. Blackbourne and colleagues evaluate the efficacy of the NoGo app in having an impact on cognitive control and in particular on inhibitory control. Compared to a control group, the authors found in people using the app an increase of the cognitive restraint evaluated with a self-report questionnaire. Regarding the exercise conveyed by the app, authors showed a significant effect in improving inhibitory control in the training group. Other measured outcomes were self-reported food consumption and attitude towards food and diet. Results demonstrated the effectiveness of the app was in improving even these aspects.

Bless and colleagues concluded that the training of auditory attention through a mobile application is feasible and successful. After 21 days of practicing, authors found an increase in auditory attention. This is supported by the fact that the training group showed an increase in the performance of the exercise itself but in brain activation measured with fMRI as well.

Finally, also Powell and colleagues directly focused on the efficacy of their mobile application. Authors evaluated its effectiveness in improving problem-solving ability, but no significant effects of the cognitive training were found in comparing an intervention group using ProSolv and a control group performing a traditional cognitive training. The remaining studies other authors decided to focus their aim on subjective evaluation of their app [28–30,32–34]. For these studies, there is a lack of data regarding the effects produced by the application on cognitive abilities.

**Discussion**

This systematic review provides a useful, clear and comprehensive overview of the current state-of-the-art on available apps for cognitive training. However, this work also posits some critical issues regarding the application of this kind of training in clinical and research practice. While some issues are broader and relevant to the field of cognitive training apps, others are more specific and directly related to their application in a cancer patient population.

**General issues in cognitive training apps**

First, the majority of the articles included in the present review has the primary aim of evaluating only app’s usability, acceptability, feasibility and users’ satisfaction, whereas only a few of them
directly focused at demonstrating their efficacy on improving cognitive functioning. Only two [25,26] out of eleven studies reports significant and quantitative amelioration in cognitive performance. Even if feasibility's dimensions is certainly a pivotal aspect, it is worthy of note that the objective efficacy of the apps has not been measured by the majority of the relevant articles. Indeed, for several apps, we could not conclude whether or not the training effectively improves the targeted cognitive domains.

Second, some definitional and conceptual issues about cognitive functions also emerge. Specifically, there is a vast heterogeneity in the definition and conceptualization of cognitive function across studies, with similar cognitive domains being labeled in different ways (e.g., executive functions may comprehend visuospatial attention, attention and so on). Moreover, targeted cognitive functions are not unique or consistent across studies with only marginal overlap between studies. Furthermore, some cognitive functions (e.g., memory) cover heterogeneous abilities (e.g., working memory, short-term memory, long-term memory) encompassing specific functions that can be selectively impaired in some diseases and not in others. Thus, it is difficult to draw conclusions on which cognitive domain could benefit or not from apps training. Given the aforementioned issues, it is critical to properly evaluate the clinical efficacy and effectiveness of these apps.

**Specific issues in cognitive training apps applied to cancer patients**

Taken together, these results show that there are apps are best candidates to target cognitive functions that are generally impaired in women with breast cancer. However, the feasibility, usefulness, and efficiency of such kind of cognitive training in this particular population should not be automatically taken for granted.

Relevant articles included in the present review, in fact, employed high heterogeneous samples of subjects: only a few apps have been tested on patients, such as people with Alzheimer [34] or with multiple sclerosis [33], others have been evaluated on a healthy general population sample of adults or children. This heterogeneity is also indicative of the different needs of these diverse populations.

People with breast cancer patients may benefit from using these available interventions or ad hoc to-be-developed apps for this specific category of patients. In fact, breast cancer patients somehow reside in a class between mildly or severely cognitively impaired patients, as they generally display objective cognitive impairments or report cognitive problems [9], and healthy general population subjects, as they still can properly work and have an active and preserved social life. On one hand, different from many other cognitive impaired patients, they do not display a degenerative disease, with a progressive worsening of global or selective cognitive functioning. On the other hand, unlike cognitive healthy individuals, they are generally aware and worried that their cognitive worsening could interfere with daily routines and everyday life. Thus, they are generally strongly motivated to be involved in a cognitive training program. Worthy of note, breast cancer patients usually display a high level of distress symptoms and serious psychological side effects [5,9], that can influence subjective perception of cognitive functioning and that could potentially interfere with training activities.

Finally, for what concern the targeted cognitive functions, the majority of the summarized papers, apart from Lu and colleagues and Shellington and colleagues [30,32] reported training interventions on a single cognitive domain. However, women with breast cancer often display difficulties and deficits in several cognitive domains. Thus, it could be relevant to design, develop and implement an ad hoc application targeting all these various cognitive function domains in breast cancer patients.
Conclusion
To date, there are no available cognitive training apps that completely meet the needs of breast cancer survivor women. Currently available apps lack strong specificity for oncological breast patients both from the point of view of the cognitive functions that should be addressed and for the psychological complexity that these patients display. In fact, the psychological and physical impact of breast cancer on cognitive impairment should be taken into account as well. Nowadays medicine is evolving considering not only the patient’s physical safety but also in prevention with a personalized approach to disease [68,69]. From the patient empowerment perspective, it is very important to give breast cancer survivors reliable means to improve and train their cognitive functioning because of the huge impact of cognitive complaints on the quality of life and patients empowerment [70]. Moreover, women with breast cancer may benefit from using a mobile or web-based tool to improve their cognitive functioning, to effectively manage their daily activity and to properly cope with everyday difficulties. This could also be especially helpful to foster breast cancer patients' perceived self-efficacy and manage their anxious and depressive symptomatology. To sum up, we may conclude that further studies should at least properly test the feasibility, usability, and effectiveness of available cognitive training apps in women with breast cancer. Moreover, because of the complexity and multi-dimensionality of the cognitive difficulties affecting this cancer population, it may be useful to design, develop and implement an ad hoc application targeting cognitive impairment in breast cancer patients.

Acknowledgments
This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 643529.

This presentation reflects the authors' view. The Commission is not responsible for any use that may be made of the information it contains.
GM and LV reviewed the literature and wrote the main part of the review. SFMP, DM, KM and GP supervised the work, reviewed the manuscript and provided conclusions.

Conflict of Interest
None declared

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