Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.ajgponline.org

Regular Research Article

Recommendations for the Nonpharmacological Treatment of Apathy in Brain Disorders

Valeria Manera, PhD, Sharon Abrahams, DClinPsy, PhD, Luis Agüera-Ortiz, MD, PhD, François Bremond, PhD, Renaud David, MD, PhD, Kaci Fairchild, PhD, Auriane Gros, PhD, Cécile Hanon, MD, Masud Husain, DPhil, FRCP, FMedSci, Alexandra König, PhD, Patricia L. Lockwood, PhD, Maribel Pino, PhD, Ratko Radakovic, CPsychol, PhD, Gabriel Robert, MD, PhD, Andrea Slachevsky, MD, PhD, Florindo Stella, MD, PhD, Anaïs Tribouillard, MSc, Pietro Davide Trimarchi, PhD, Frans Verhey, MD, PhD, Jerome Yesavage, MD, PhD, Radia Zeghari, MSc, Philippe Robert, MD, PhD

From the Université Côte d'Azur, CoBTeK lab (VM, FB, RD, AG, AK,AT, RZ, PR), Nice, France; Association Innovation Alzheimer (VM, PR), Nice, France; School of Philosophy, Psychology and Language Sciences (SA), University of Edinburgh, Edinburgh, United Kingdom; Euan MacDonald Centre for Motor Neurone Disease Research (SA, RR), University of Edinburgh, Edinburgh, United Kingdom; Department of Psychiatry (LA-O), Instituto de Investigación Sanitaria (imas12), Hospital Universitario 12 de Octubre & CIBERSAM, Madrid, Spain; INRIA (FB, AK), STARS Team, Sophia Antipolis, France; Centre Hospitalier Universitaire (CHU) de Nice (RD, PR), CMRR, Nice, France; Department of Veterans Affairs (KF, JY), VA Palo Alto Health Care System, CA; Department of Psychiatry and Behavioral Sciences (KF, JY), Stanford University School of Medicine, CA; Psychiatric Department, Regional Resource Center of Old Age Psychiatry Corentin-Celton Hospital (CH), Academic Hospital West Paris, AP-HP, Paris Descartes University, Sorbonne Paris Cité, Paris, France; Nuffield Department of Clinical Neurosciences (MH, PL), John Radcliffe Hospital Oxford OX3 9DU, United Kingdom; Department of Experimental Psychology (MH, PL), University of Oxford, Oxford, United Kingdom; Wellcome Centre for Integrative Neuroimaging (MH, PL), University of Oxford, Oxford, United Kingdom; Broca Living Lab (MP), AP-HP, Paris Descartes University, Sorbonne Paris Cite, Paris, France; Faculty of Medicine and Health Sciences (RR), University of East Anglia, Norwich, United Kingdom; Alzheimer Scotland Dementia Research Centre (RR), University of Edinburgh, Edinburgh, United Kingdom; EA4712 "Comportement et Noyaux Gris Centraux" (GR), Université de Rennes1, France; Geroscience Center for Brain Health and Metabolism (GERO) (AS), Faculty of Medicine, University of Chile, Santiago, Chile; Neuropsychology and Clinical Neuroscience Laboratory (LANNEC) (AS), Physiopathology Department - ICBM, Chile; Neuroscience and East Neuroscience Departments (AS), Faculty of Medicine, University of Chile, Chile; Memory and Neuropsychiatric Clinic (CMYN) Neurology Department (AS), Hospital del Salvador and Faculty of Medicine, University of Chile, Santiago, Chile; Servicio de Neurología (AS), Departamento de Medicina, Clínica Alemana-Universidad del Desarrollo, Santiago, Chile; Laboratório de Neurociências LIM27 (FS), Departamento e Instituto de Psiquiatria, Hospital das Clínicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, SP, Brasil; UNESP − Universidade Estadual Paulista (FS), Biosciences Institute, Campus of Rio Claro, Rio Claro, SP, Brazil; ISTR (AT), Institute of Rehabilitation Sciences and Techniques, University of Lyon 1, Lyon, France; Specialised Alzheimer Team (AT), SSIAD Quimper, France; IRCCS Fondazione Don Carlo Gnocchi (PDT), Milan, Italy; and the Department of Psychiatry and Neuropsychology (FV), Maastricht University, School for Mental Health and Neuroscience (MHeNs), Alzheimer Center Limburg, Maastricht, the Netherlands. Send correspondence and reprint requests to Valeria Manera, CoBTeK lab - Université Côte d'Azur, Institut Claude Pompidou, 10 rue Molière 06100, Nice, France.
e-mail: Valeria.manera@unice.fr

Implications for Practice and Research: NPT should be tailored to deficits (e.g., cognitive, physical), clinical objectives (e.g., prevention, intervention) and preferences (e.g., personal, sensory) of each patient. ICT may help to improve treatment personalization, increase motivation, and aid remote treatment delivery. Further structured research (e.g., RCT) is needed to determine NPT efficacy.

https://doi.org/10.1016/j.jagp.2019.07.014

ARTICLE INFO

Article history:
Received May, 28 2019
Revised July, 26 2019
Accepted July, 26 2019

Key Words:
Apathy
motivation
complementary therapies
prescriptions
nondrug
ICT
brain disorders

ABSTRACT

Apathy is a common neuropsychiatric syndrome observed across many neurocognitive and psychiatric disorders. Although there are currently no definitive standard therapies for the treatment of apathy, nonpharmacological treatment (NPT) is often considered to be at the forefront of clinical management. However, guidelines on how to select, prescribe, and administer NPT in clinical practice are lacking. Furthermore, although new Information and Communication Technologies (ICT) are beginning to be employed in NPT, their role is still unclear. The objective of the present work is to provide recommendations for the use of NPT for apathy, and to discuss the role of ICT in this domain, based on opinions gathered from experts in the field. The expert panel included 20 researchers and healthcare professionals working on brain disorders and apathy. Following a standard Delphi methodology, experts answered questions via several rounds of web-surveys, and then discussed the results in a plenary meeting. The experts suggested that NPT are useful to consider as therapy for people presenting with different neurocognitive and psychiatric diseases at all stages, with evidence of apathy across domains. The presence of a therapist and/or a caregiver is important in delivering NPT effectively, but parts of the treatment may be performed by the patient alone. NPT can be delivered both in clinical settings and at home. However, while remote treatment delivery may be cost and time-effective, it should be considered with caution, and tailored based on the patient's cognitive and physical profile and living conditions. (Am J Geriatr Psychiatry 2019; ■■:■■–■■)

INTRODUCTION

In various brain disorders, apathy is consistently defined as a multidimensional syndrome characterized by a significant reduction in goal-directed activity.[1–5] Different apathy dimensions or subtypes include symptoms in relation to behavior (reduced level of activity and initiative), cognition (reduced interests and motivation for planning), emotions (emotional blunting, indifference, and affective flattening), and social interaction (reduced social activities and engagement).[3–5] Apathy is prevalent across many neurocognitive disorders (NCD, DSM-5[6]) and psychiatric disorders. It represents the most common behavioral and psychological symptom in people with Alzheimer disease (AD) and is often observed in Parkinson disease (PD), vascular dementia, stroke, traumatic brain injury, amyotrophic lateral sclerosis/motor neurone disease (ALS/MND), frontotemporal dementia, progressive supranuclear palsy, small vessel disease, major depression and schizophrenia.[7]

Pharmacological therapies have demonstrated limited efficacy in the management of apathy associated with NCD and neuropsychiatric conditions. Methylphenidate has been observed as potentially beneficial in reducing levels of apathy in people with AD, and rivastigmine may be beneficial for people with PD, but these findings are associated with weak evidence.[8,9] Nonpharmacological treatment (NPT) – or *ecopsychosocial* interventions[10] – are often considered to be at the forefront of apathy management.[11] NPTs aim to address the cognitive, psychological, social, personal, and relational functioning of the person. Usually these interventions use a "person-centered" rather than a "symptom-centered" approach, since they address not only the primary symptoms of a condition, but also the secondary experiences that arise as a consequence of the condition.[12] NPTs include a wide range of methods, such as group activities, therapeutic dialogs, meditation, and sensory, physical, and physiological stimulation (Table 1). The scope of NPTs is broad and covers different dimensions such as cognition, motor skills, functional abilities, psychobehavioral symptoms, social life, and self-esteem. The general goals of these types of interventions are to

TABLE 1. Different Types of NPT Used in Different Populations With Apathy as a Direct or Indirect Target

Approach	Description of the Intervention	Mainly Used in
Art Therapy	Form of psychotherapy that uses art media as its primary mode of communication to enable a patient to change and grow on a personal level through the use of art materials in a safe and facilitating environment.	Mild and Major NCD (including AD, all stages)[11]
Cognitive interventions	Cognitive stimulation, training or rehabilitation designed to solicit one or more cognitive functions such as attention, memory, language, orientation to maintain, improve or compensate for them. This includes both classical and computerized interventions (e.g., serious-games).	Mild and Major NCD;[17,18] PSP;[19] Schizophrenia;[20] PD;[21] and Acute Stroke[22]
Animal assisted Therapy (AAT)	Based on patient-animal-therapist interaction, AAT is an individual or group intervention carried out in care settings by a professional to improve mental, cognitive, physical, social and/or emotional functioning of patient.	AD (moderate stage)[23]
Motivational Interviewing	Collaborative client-centered approach designed to enhance internal motivation for behavior change through the reduction of patient ambivalence feelings. It is based on several social and behavioral principles such as empathy, decisional balance and reduction of resistance to change.	TBI[24]
Physiotherapy	Science-based profession aimed to help people affected by injury, illness or disability through movement and exercise, manual therapy, education and advice.	Acute Stroke,[25] and PD[26]
Multi-sensory Stimulation/Snoezelen	Person-centered care approach using i.e., lights, aroma therapy, music/sounds, tactile objects, and/or screen projectors in an immersive environment to actively stimulate one or more of the different senses (vision, audition, tact, olfaction and taste).	Major NCD[11]
Music therapy	Clinical active or receptive interventions using music, its instruments and properties in individual or group settings to optimize people's quality of life and improve their different functions (physical, social, communicative, emotional, intellectual).	Mild and Major NCD (including AD, all stages)[11]
Occupational therapy (OT) interventions	In a client-centered care approach, OT accompanies people encountering disability situations in order to improve, maintain or compensate their participation in activities of daily living. With regards to Apathy, OT can provide the patient and his/her caregiver with more engaging and personalized strategies and a program of tailored activities, customized to previous and current interests, residual functional capacities and patient's level of cognitive decline.	Mild and Major NCD (including AD, all stages);[11,27,28] and PD[29]
Physical activity	Physical exercise can have positive effects on both physical function and mental health. Physical exercise can aim to improve muscle strengths (lower and upper limbs), balance, mobility, and reduce stress. Examples of activities include: strengthening and balance exercises, cycling, swimming, yoga and Pilates.	PD;[26] Major NCD, and Stroke[30]
Reminiscence	Therapy based on the evocation and discussion about personal past activities, events and life experiences, in individual or group settings, using a variety of supporting meaningful materials.	Major NCD (including AD, all stages)[11]
Assistive social robots	Therapeutic or recreational interventions that use social robots (animal-like, human-like) as a support to promote communication, reduce loneliness and improve the emotional state of the user.	Major NCD[11]
Staff or caregiver education program	The learning of behavioral strategies to manage apathy in care settings or in-home care and reduce its negative consequences.	Neurological conditions (AD, PD, etc.);[31] Mild NCD;[27] and PSP[19]
Virtual Reality (VR)	VR is an ICT used in healthcare settings to help diagnosis or to treat cognitive, psychological or physical pathologies. Its strengths consist of ecological validity, which can facilitate the transfer of VR learning to the real world, its ludic aspect and the possibility of personalization of the immersive environment.	Mild NCD[32]
Repetitive Transcranial Magnetic Stimulation (rTMS)	Noninvasive treatment consisting of magnetic stimulation sessions using a figure-of-eight-shaped coil applied on a target cranial surface in order to increase cortical activity and modulate cerebral networks.	Mild NCD;[33] PD;[34] and Chronic stroke[35]

AD: Alzheimer's disease; NCD: neurocognitive disorder; PD: Parkinson's disease; PSP: progressive supranuclear palsy; TBI: traumatic brain injury.

strengthen cognitive, psycho-affective, and social skills to reduce psycho-behavioral symptoms, to preserve the patient's social activity, to restore confidence and self-esteem, and to promote autonomy as well as quality of life.[13]

A variety of NPTs (symptom specific and symptom nonspecific) have proven useful for the treatment of apathy. In people with Mild and Major NCD, for example, NPTs have been shown to be effective in improving apathy administered alone[11] or combined with drug therapy.[14,15] A summary of the NPTs employed to reduce apathy (as a direct or indirect target), and the clinical populations on which they have been employed is presented in Table 1 (see[11,14,16] for more exhaustive reviews).

Information and Communication Technologies (ICT) have also started to be employed in NPTs to train cognitive and physical functions, promote communication, reduce loneliness and improve the emotional state in apathetic and nonapathetic patients. These include, Virtual Reality (VR),[32] Serious Games (i.e., video-games designed to train cognitive and/or physical functions[18,36]), and social robots.[11] Remote NPT delivery through telemedicine interfaces is also starting to be explored for elderly people with cognitive impairment.[37]

Although most studies of NPTs have demonstrated promising results, the improvements in apathy do not seem long lasting (from 1 week to several months, depending on the study),[38] and results have been difficult to reproduce due to variability in the treatment delivery and conditions.[11] In most of the existing Randomized Controlled Trials (RCT), apathy was not the primary intervention target and the main endpoint. Similarly, apathy was rarely measured using multidimensional scales. The wide variability in sample size, diagnosis, apathy assessment, follow-up duration, and intervention conditions make it hard to provide strong conclusions on NPT efficacy in apathy management.[7] The field would benefit from more well-designed clinical studies (RCT) employing apathy as the main endpoint. These studies could focus on understanding which treatments are most effective for different pathologies, and in which conditions, as well as where, when, and how often they should be implemented. The objective of the present work was to gather recommendations from experts in the field concerning the use of NPTs for apathy, and the role of ICT in delivering NPTs.

METHODS

The task force included 20 experts (researchers and healthcare professionals) in the domain of apathy in NCD and psychiatric disorders. The experts were from 8 different countries (France, United Kingdom, USA, Italy, Brazil, Spain, Chile, and the Netherlands). The experts' main professional backgrounds were Psychiatry (N = 8), Psychology (N = 8), Neurology (N = 2), Speech Therapy (N = 1), and ICT (N = 1). All of them had more than 5 years of experience in the domain of apathy (9 participants with 5−10 years of experience, 5 participants with 10−20 years of experience, and 6 participants with more than 20 years of experience). Following a standard Delphi methodology,[39] the recommendations were developed in a two-step process: web-surveys followed by a consensus meeting.

Web-surveys

The experts were asked to answer questions via a web-survey in three rounds (between November 2018 and March 2019) using Microsoft Forms. After each round, a facilitator (PR) provided a summary of the experts' responses, and encouraged the experts to analyze, comment, and (eventually) revise their earlier responses considering the commentaries of other members of the panel. Questions in the three rounds included 13 rating questions (Supplementary Table 1): 9 (questions 1−9) focused on classical NPTs, 4 (questions 10−13) on the use of new ICT in NPT. For each question, participants rated their degree of agreement by employing a five-point Likert scale (1 = not important/pertinent at all; 2 = not very important/pertinent; 3 = important/Pertinent; 4 = very important/pertinent; and 5 = extremely important/pertinent). After each rating question, participants could provide comments. Round 1 also included the following open question: "Please report the 3 most important limitations and benefits of using ICT in NPT for apathy." The list of reported benefits and limitations was employed as a starting point to perform a SWOT analysis (Strengths, Weaknesses, Opportunities, and Threats) of the use of ICT for NPTs. Several open questions were asked in rounds 2 and 3 to comment on the responses provided in rounds 1 and 2. After round 2, a first draft of the recommendations was circulated among the experts.

Final Consensus Meeting

The three web-surveys' results and the open discussion points were revised by the task force during a plenary meeting held on March 8, 2019 in Nice (France).

RESULTS

The results of the rating questions (median and interquartile range) are reported in Supplementary Table 1. The number of responses obtained for each question ranged from 14 to 16.

General Questions

NPT for whom (Q1). The experts reported that NPTs for apathy are "extremely important" for patients with Major NCD (defined in the DSM-5 as a significant cognitive decline interfering in the independence of the individual with relation to everyday activities due to pathologies including AD, PD, and other neurodegenerative disorders), and "very important" for people with schizophrenia or psychotic disorders, depressive disorders, and Mild NCD (defined in the DSM-5 as a noticeable decrement in cognitive functioning that goes beyond normal changes seen in aging, with independence and autonomy is activities of daily living preserved thanks to compensatory strategies). Apathy NPTs were rated as "important" for people with Post-Traumatic Stress Disorders, and subjective cognitive decline (SCD, characterized by cognitive complaints associated to unimpaired performance on cognitive tests). The difference in level of importance was reported mainly because apathy shows a higher prevalence in patients with severe impairments.[40,41] The experts also considered NPTs to be important for targeting apathy in the context of limbic and paralimbic tumors, personality disorders, Traumatic Brain Injury, stroke, small vessel disease, and ALS/MND.

NPT for what (Q2). Participants considered apathy NPTs to be "extremely important" or "important" for patients presenting symptoms in the different dimensions listed in the 2018 Diagnostic Criteria for Apathy (DCA), namely behavior or cognition, emotion and social interaction.[3] Apathy is consistently described as a multidimensional construct, and it is recognized that different apathy dimensions may be differently impaired in different pathologies[5,41] and have different neural substrates.[42] Different NPTs may be suitable to help those with impairments in different apathy dimensions. However, there is not enough evidence suggesting differential efficacy of NPTs for specific apathy dimensions, as studies typically employ global apathy measures only.[11] In addition, there is still no final consensus on the number and type of apathy dimensions, meaning that different apathy scales capture different apathy dimensions.[43–45] The experts acknowledged the need and importance for further research in order to converge in the understanding of the construct of apathy. Additionally, experts acknowledged the need to determine whether NPT treatments targeting specific apathy dimensions may also be useful to target conditions showing a partial overlap with apathy, such as anhedonia, depression, and chronic fatigue.[7]

NPT based on what. When asked what factors are the most important for selecting the best NPT (Q3), the level of severity of the disease (cognitive and functional impairment) was rated as "extremely important," while the age of the patient and the environment and lifestyle were rated as "very important." Participants acknowledged that it is "extremely important" to choose NPT based on the personal interests and sensory preferences (e.g., favorite colors, music, odors; Q4). This is in line with previous research suggesting that personalized interventions are a key aspect to improve or maintain treatment adherence and efficacy.[11] The most appropriate methods to collect patient's needs and interests (Q5) were structured and semistructured interviews, ICT, and Serious Games (very appropriate), while open questions were rated as between "appropriate" and "very appropriate." The most appropriate methods to collect patients' *sensory* preferences (Q6) were observation by exposure, semistructured interviews, and ICT or serious games (very appropriate), while assessment performed by others (clinicians or caregivers) was rated between "appropriate" and "very appropriate," and self-evaluation as "appropriate." The experts highlighted the importance of developing standardized tests to collect patients' sensory preferences, which should be validated and compared to what is obtained in observation by exposure or observed in routine care.

Multisensory interventions, in which several senses are stimulated simultaneously, have showed promising results in reducing apathy,[11] however, which (and how many) senses should be stimulated is still debated.[46] Participants reported that in multisensory interventions, it is "very appropriate" to stimulate sight, hearing, smell, and touch, and that stimulating taste is rated as between "appropriate" and "very appropriate" (Q7), mainly due to difficulties in materials available (e.g., the use of foods and drinks in a therapeutic setting).

NPT with whom. In Q8 participants reported that it is "very pertinent" to administer NPT in individual sessions, while it is "pertinent" to administer them in group sessions. The preference for individual sessions was mainly explained by the need for achieving personalized objectives. Patients with different types and degrees of impairment, different deficits, and different personal preferences should be stimulated in different ways. However, group sessions might be relevant to stimulate social interactions. The presence of a therapist (physical or virtual) was reported as a key element in designing NPT. Indeed, the interaction with the therapist can promote positive emotions and affect, which can be useful in facilitating patients' motivation and maintain engagement in the treatment. But it was acknowledged that the therapist would not necessarily have to be present continuously. For instance, through ICT, patients may also continue treatment sessions alone.[18]

When. To decide if and when to prescribe or administer NPT for apathy (Q9), participants reported that it is "extremely important" that the patient and/or caregivers consider apathy as a problem. The availability of NPT adapted to the patient's needs, the patient's willingness to adhere to the NPT and the stage of the disease were rated as "very important". It was acknowledged that the decision of whether to propose NPT for apathy should be taken by clinicians in collaboration with patients and caregivers. Therefore, it is important to examine the mechanisms that lead to apathy, and not see apathy as a symptom that always requires treatment. For instance, apathy in people at the end of life may not be appropriate to target for therapeutic intervention.

Questions Focused on ICT

ICT for NPT. Participants reported that ICT is "very appropriate" for apathy NPT (Q10). All participants (N = 15) agreed that there is a good benefit or risk ratio in using ICT for apathy NPT, and 13 participants out of 15 agreed that ICT can be used to continue or maintain adherence to the intervention without the presence of the therapist. As detailed below, the experts highlighted the importance of considering the degree of patients' cognitive and functional impairment in order to evaluate the usability of ICT-based NPT. The presence of a caregiver was considered as critical for people with advanced impairment at the cognitive and functional level.

Telemedicine platforms. Participants reported that it is "very appropriate" to deliver NPT remotely by employing ICTs, such as tele-medicine platforms and VR environments (Q11) for individual sessions, while it is "adapted" for group sessions. Video-conference, audio-conference, VR immersive environments and the use of a virtual coach were all rated as "very appropriate" to deliver NPT treatments remotely (Q12), with the lowest scores (appropriate) assigned to audio-conference platforms. Based on ongoing clinical trials, the experts suggested that the selected platform should allow monitoring online of a patient's reactions to treatment, as well as to verify that the patient is following the treatment correctly.[37] The decision of which platform to employ should be taken based on which elements are important to capture. For instance, in physical training it is important that patient and therapist can see each other. However, a VR interface in which patient and therapist can share a screen may be more adapted for cognitive training sessions.

Concerning the delivery of NPTs remotely (Q13), the presence of a caregiver was rated as "very important," in order to guarantee the system usability, safety, and efficacy. The level of cognitive and functional impairment of the patient and his or her familiarity with ICT were rated between "important" and "very important" (learning to employ ICT may be part of the patients' training, depending on their level of cognitive impairment). Where the patient lives (e.g., distance from clinical facilities) was rated as "important", and home-based and/or long-term frequent treatments delivered remotely may be more convenient.

SWOT Analysis of ICT for NPT

A SWOT analysis of the use of ICT for NPTs is reported in Table 2.

Strengths. ICT can help in standardizing the treatment conditions (e.g., reproducibility, contents, and automatic follow-up), and collecting noninvasive objective, measurable, and longitudinal data on participants' adherence to treatment and their performance. Also, ICT is useful to tailor and personalize the intervention. Compared to classical treatments, ICT interventions are easier to adapt to the personal interests (e.g., serious games to train executive functions based on a cooking plot versus a naval battle plot), sensory preferences (e.g., background color of ICT interface), the level of impairment (e.g., through algorithms that adapt the game difficulty online, in what has been defined closed-loop cognition[47]), and patient's equipment (e.g., tablets, smartphones, or VR headsets). Furthermore, ICT can provide more immersive, stimulating, and varied treatments with the potential to result in higher engagement and positive emotions. Finally, ICT can provide affordable and easy to use options that can also be potentially used remotely.

Weaknesses. Some ICT interfaces are not easy to install and use, especially for older adults, Relatedly, older adults may have a negative perception of ICT, as well as negative feelings engendered through not being able to use ICT. Furthermore, social interaction may be reduced by using NPT remotely. The presence of a therapist (and/or a caregiver) is a prerequisite to mediate adherence to treatment, especially for people with more severe cognitive and functional impairment, and anosognosia. Also, newly released products can have high costs. In addition, not all high-tech interfaces are appropriate for people with

TABLE 2. Summary of a SWOT Analysis of Using ICT for Apathy NPT

Strengths	Weaknesses
- Can facilitate reproducibility and standardization (contents and automatic follow-up) - Increased ecological validity, can put a patient in a 'reality-like' setting but more controlled - Possibility to record patient activity and adherence to treatment automatically, longitudinally and remotely, on-line or off-line; - Possibility to record and analyze several ''indirect'' data (voice, movements, etc.) - Adaptation to the user (e.g., impairment type and level, personal interest) - Increased variety of activities, and easy content adaptation (themes, ergonomics) to increase engagement - Flexibility of use (multiple supports: tablet, smartphone, computer, tv screen...) - Can increase motivation, curiosity, immersion and positive emotions - Can stimulate attention and other cognitive processes in a controlled environment - Useful for long training sessions, allowing to extend patient activity at home - Cost-effectiveness (e.g., tablets, actigraphy) - Easy setup (for some devices) - No requirement of a therapist to be present all the time - Can be used for group stimulations	- Time-consuming setup (for some devices) - ICT interfaces and software difficult to use - Poor understanding (and fear of not understanding) of the technology - Need of patients' and staff's training - Need of caregivers' implication for people with Major Neurocognitive Disorder - Expensive equipment (e.g., VR headsets) - Absence of human contact (risk of reducing the opportunities of social interaction) - Possibility of poor engagement/interest - Games not embedding cognitive challenges - Games potentially not appropriate for participant's cognitive profile and culture - Lack of generalization to patient's environment (activities far from reality) - Side effects such as hallucinations, loss of sense of reality (e.g., for Virtual Reality) - Risk of accidents (e.g., risk of falls, increased sleep disturbances) - Risk of addiction - Low standardization
Opportunities	**Threats**
- Emerging advances in technology - Good accessibility for users, also remotely (at home or in remote clinical facilities) - Increasing number of seniors commonly using ICT - Could help reducing barriers in access to care in middle- and low-income countries with limited access to neuropsychiatric centers - Usable at large scale - Can be used trans-diagnostically - Can facilitate training sessions for therapists	- Long and expensive technical development, difficult to modify - Low experience in ICT by users - Cognitive/behavioral fundamentals of the classical therapies are not fully reproduced - Not enough research evidence toward effectiveness, risk and impact. - Absence of cross-cultural validation of NPT, and inappropriate adoption in nonadapted cultural domains. - Unrealistic belief that ICT can remedy everything - Digital divide - Poor acceptance in the medical community

cognitive impairment, or for specific cultural backgrounds, and may not embed challenges that make the training engaging. However, these aspects can be improved by designing interfaces tailored to specific categories of patients and deficits.[36] Finally, similar to classical NPT, there is a risk of accidents with remote training (e.g., risk of falls for physical activity trainings), and potentially a risk of addictive or habitual behavior, specifically linked to the use of video-games.

Opportunities. ICT is becoming increasingly affordable and easier to use. In parallel, its adoption is dramatically increasing (ESA, 2017). These trends represent opportunities for giving wider accessibility to NPT for people with apathy. Through delivering ICT-based NPT remotely, this would allow people living rurally, far from clinical facilities and/or with mobility problems, and eventually people living in middle- and low-income countries with limited access to neuropsychiatric centers, to get easier access to care. Also, ICT may help to deliver NPT at a large scale, and facilitate trainings for therapists, resulting in more standardized treatments.

Threats. ICT-based NPT (e.g., serious games, VR) often requires a long, expensive technical development and can be difficult to modify once it is released. Also, there is currently insufficient consistent evidence regarding the effectiveness, risk and impact, as well as cross-cultural validation of both classical and ICT-based NPT. Due to these limitations, ICT-based NPTs often result in poor acceptance in the medical community.[48]

DISCUSSION

NPTs are currently employed as frontline treatments for apathy in people with different brain disorders[11] and previously reported NPTs have shown initial promising results in improving apathy (Table 1). However, the field urgently needs more methodologically sound studies (RCT) to assess the efficacy of specific NPTs, and to standardize treatment materials and conditions. Here, we gathered recommendations from experts on how to progress the field further. Converging with previous studies, our results suggested several important implications for clinical practice and research.

Early detection of apathy. In NCD apathy can appear at the early stages of the disease progression.[49] Apathy is recognized as a multidimensional construct; reduction in goal-directed activities can be found in the domains of behavior, cognition, emotions, and social interaction.[3] To implement early interventions, it is necessary to assess apathy early in the disease progression. The experts suggested that more collaborative research would be needed for further convergence of understanding of the construct of apathy. The 2018 DCA[3] may be particularly useful in this context, as they are 1) transdiagnostic, making it possible to compare apathy in different populations, and 2) multidimensional, providing a method to obtain a composite apathy profile. Furthermore, 3) they form the basis for potential clinical scales and ICT-based instruments to detect each apathy dimension. Employing the 2018 DCA in the clinical practice may contribute to increasing comparability of results across clinical centers. Crucially, the experts recommended that future studies employ multidimensional apathy assessment (e.g., Apathy Motivation Index;[43] Dimensional Apathy Scale[44,45]) to better understand the differential effects of different NPT. Finally, impairments in apathy dimensions should also be reported for patients not fulfilling the DCA. Indeed, isolated symptoms such as lack of interest and/or social interaction are also found in a significant proportion of individuals without clinical apathy.[41] The presence of some isolated symptoms − for instance lack of interest − may be due to a partial overlap between apathy and other clinical conditions, such as depression.[4] However, symptoms may also appear in isolation and independently of these conditions. Knowing which isolated symptoms preceded − for months or years − an apathy diagnosis would help to better understand how apathy develops and unfolds over time.

Early intervention. In clinical settings, symptom-specific and nonspecific NPTs for apathy are more commonly employed in people with well-established pathological conditions.[11] However, in NCD apathy can appear at the early stages of the disease progression, even in people with SCD. The presence of apathy has been associated with a faster cognitive and functional decline,[50] representing a risk factor for the conversion from Mild Cognitive Impairment (MCI) to AD.[51] Critically, preliminary evidence suggests that interventions targeting apathy in people with MCI (e.g., with repetitive transcranial magnetic stimulation) may be effective in improving the global cognitive functioning.[33] Thus, putting in place early treatment options for MCI or even SCD might offer new opportunities for altering the trajectory of Alzheimer's disease dementia. Apathy has

also been observed as prevalent in early stages of other neurodegenerative conditions, such as PD[52] and ALS/MND.[53] Therefore, an important area for future investigation is the development of NPTs for apathy at the early stages of disease processes.

Personalized therapy. Generic approaches to activities may fail to produce positive changes in many patients: the more the treatment is tailored to the person, the higher the probability that the treatment is effective.[54] At a clinical level, "tailor-made" approaches are required, including designing specific meaningful activities depending on individuals' interests, needs, abilities, and capacities,[55] and in line with their perceived self and identity.[56] Sensory preferences (e.g., what the person likes to touch, smell, eat, his or her favorite colors and music) of the person are also important aspects to consider. Further, collecting personal interests, needs, preferences, and identities are not trivial when dealing with people with neurocognitive and neuropsychiatric disorders. At a research level, it is important to develop instruments that would be able to capture these aforementioned preference dimensions in a standardized way. Semistructured interviews and serious games represent such promising instruments.

The role of ICT. In line with previous recommendations,[48,57] the experts suggested that ICT may play an important role in NPT for apathy. The use of ICT in NPT for apathy is still in an early phase of development, characterized by encouraging initial research results.[48] The many listed strengths − including improving treatment standardization, noninvasive and continuous monitoring of patients' apathy, and remote treatment delivery − provide a justification for further development of ICT as NPT for apathy. However, some weaknesses were noted (in particular concerning the difficulty that older patients experience with using ICT alone), as well as some threats, none of which were deemed to be major. At the practical level, it would be important to develop easy-to-use, affordable ICT solutions for clinicians that can be implemented in everyday practice, and potentially be employed remotely, with the help of a caregiver. At a research level, it is important to collect methodologically sound data to test and evolve usability, usefulness, and efficacy of ICT-based NPTs targeting people with brain disorders.

In summary, through expert consensus, improving early detection and early treatment may be valuable in characterizing and managing apathy as a syndrome in brain disorders. Furthermore, personalized NPT approaches for apathy may provide stronger evidence of NPT efficacy, which would result in clearer guidelines for NPT prescription or administration and delivery. ICT may play a role in facilitating NPT delivery, standardization, and assessment; provide a potential future avenue for development methods of management, treatment, and interventions for apathy.

MH is funded by The Wellcome Trust and NIHR Oxford BRC. Concerning conflicts of interest, the only one to report is the following: GR reports personal fees and non-financial support from Otsuka-Lundbeck, personal fees and non-financial support from Janssen, outside the submitted work. All the other authors have nothing to disclose.

This work was supported by the Association IA, the JL Noisiez Fondation, and by the French government, through the UCA-JEDI "Investments in the Future" project managed by the National Research Agency (ANR) with reference number ANR-15-IDEX-01. The recommendations were drafted in the context of the MNC3 program. RR was supported by Motor Neurone Disease Association and Motor Neurone Disease Scotland. AS was supported by FONDAPprogram grant 15150012. MH is funded by The Wellcome Trust and NIHR Oxford BRC.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.jagp.2019.07.014.

References

1. Marin R: Apathy: a neuropsychiatric syndrome. J Neuropsychiatry Clin Neurosci 1991; 3:243–254
2. Robert P, Onyike C, Leentjens A, et al: Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. Eur Psychiatry 2009; 24:98–104
3. Robert P, Lanctôt K, Agüera-Ortiz L, et al: Revision of the diagnostic criteria for apathy in brain disorders: the 2018 International Consensus Group. Eur Psychiatry 2018; 54:71–76
4. Levy R, Dubois B: Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. Cereb Cortex 2006; 16:916–928
5. Radakovic R, Abrahams S: Multidimensional apathy: evidence from neurodegenerative disease. Curr Opin Behav Sci 2018; 22:42–49
6. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders. 5th ed Arlington, VA: Author, 2013

7. Husain M, Roiser JP: Neuroscience of apathy and anhedonia: a transdiagnostic approach. Nat Rev Neurosci 2018; 19:470–484
8. Ruthirakuhan MT, Herrmann N, Abraham EH, et al: Pharmacological interventions for apathy in Alzheimer's disease. Cochrane Database Syst Rev 2018;doi:10.1002/14651858.CD012197.pub2
9. Seppi K, Ray Chaudhuri K, Coelho M, et al: Update on treatments for nonmotor symptoms of Parkinson's disease—an evidence−based medicine review. Mov Disord 2019; 34:180–198; doi:10.1002/mds.27602
10. Zeisel J, Reisberg B, Whitehouse P, et al: Ecopsychosocial interventions in cognitive decline and dementia: a new terminology and a new paradigm. Am J Alzheimers Dis Other Demen 2016; 31:502–507;doi:10.1177/1533317516650806
11. Theleritis C, Siarkos K, Politis AA, et al: A systematic review of non-pharmacological treatments for apathy in dementia. Int J Geriatr Psychiatry 2018; 33:e177–e192 https://doi.org/10.1002/gps.4783
12. Turton W: An introduction to psychosocial interventions. In: Walker S, ed. Psychosocial Interventions in Mental Health Nursing, SAGE. Learning Matters, 2014. (4-21)
13. Zuchella C, Sinforiani E, Tamburin S, et al: The multidisciplinary approach to Alzheimer's disease and dementia. A narrative review of non-pharmacological treatment. Front Neurol 2018 https://doi.org/10.3389/fneur.2018.01058
14. De Oliveira AM, Radanovic M, de Mello PCH, et al: Nonpharmacological interventions to reduce behavioral and psychological symptoms of dementia: a systematic review. BioMed Res Int 2015; 2015, Internet[cited 2018 Sep 23]Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4676992/
15. Scales K, Zimmerman S, Miller SJ: Evidence-based nonpharmacological practices to address behavioral and psychological symptoms of dementia. Gerontologist 2018; 58(suppl_1):S88–S102, Internet[cited 2018 Aug 15]Available from: https://academic.oup.com/gerontologist/article/58/suppl_1/S88/4816740
16. Olley R, Morales A: Systematic review of evidence underpinning non-pharmacological therapies in dementia. Aust Health Rev 2018; 42:361., Internet[cited 2018 Sep 23]Available from: http://www.publish.csiro.au/?paper=AH16212
17. Buettner LL, Fitzsimmons S, Atav S, et al: Cognitive stimulation for apathy in probable early-stage Alzheimer's. J Aging Res 2011 https://doi.org/10.4061/2011/480890
18. Manera V, Petit P-D, Derreumaux A, et al: 'Kitchen and cooking,' a serious game for mild cognitive impairment and Alzheimer's disease: a pilot study. Front Aging Neurosci 2015; 7:24; doi:10.3389/fnagi.2015.00024
19. Rittman T, Coyle-Gilchrist IT, Rowe JB: Managing cognition in progressive supranuclear palsy. Neurodegener Dis Manag 2016; 6:499–508 https://doi.org/10.2217/nmt-2016-0027
20. Raffard S, Gutierrez L-A, Yazbek H, et al: Working memory deficit as a risk factor for severe apathy in schizophrenia: a 1-year longitudinal study. Schizophr Bull 2016; 42(3):642–651 https://doi.org/10.1093/schbul/sbw002
21. Daniele A, Panza F: Can a cognitive rehabilitation program in early stages of Parkinson's disease improve cognition, apathy and brain functional connectivity for up to 18 months? Eur J Neurol 2018; 25:203–204 https://doi.org/10.1111/ene.13542
22. Mikami K, Jorge RE, Moser DJ, et al: Prevention of poststroke apathy using escitalopram or problem-solving therapy. Am J Geriatr Psychiatry 2013; 21:855–862 https://doi.org/10.1016/j.jagp.2012.07.003
23. Garzon E, Sillou J-M: Animal assisted therapy and Alzheimer disease: improving on the apathy of patients in nursing home. La Revue de Gériatrie 2014; 39:429–438, Retrieved from http://www.revuedegeriatrie.fr/index.php
24. Lane-Brown A, Tate R: Evaluation of an intervention for apathy after traumatic brain injury: a multiple-baseline, single-case experimental design. J Head Trauma Rehabil 2010; 11:459–469
25. Chen L, Xiong S, Liu Y, et al: Comparison of Motor Relearning Program versus Bobath approach for prevention of poststroke apathy: a randomized controlled trial. J Stroke Cerebrovasc Dis 2019; 28:655–664 https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.11.011
26. Subramanian I: Complementary and alternative medicine and exercise in nonmotor symptoms of Parkinson's disease. Int Rev Neurobiol 2017; 134:1163–1188 https://doi.org/10.1016/bs.irn.2017.05.037
27. Adam S, De Linden MV, Juillerat A-C, et al: The cognitive management of daily life activities in patients with mild to moderate Alzheimer's disease in a day care centre: a case report. Neuropsychol Rehabil 2000; 10:485–509 https://doi.org/10.1080/096020100501435568
28. Goris ED, Ansel KN, Schutte DL: Quantitative systematic review of the effects of non-pharmacological interventions on reducing apathy in persons with dementia. J Adv Nurs 2016; 72:2612–2628 https://doi.org/10.1111/jan.13026
29. Leroi I, David R, Robert PH: Apathy in Parkinson's Disease. Psychiatry Parkinson's Dis 2012; 27:27–40 https://doi.org/10.1159/000331524
30. Telenius EW, Engedal K, Bergland A: Effect of a high-intensity exercise program on physical function and mental health in nursing home residents with dementia: an assessor blinded randomized controlled trial. PLoS One 2015; 10:e0126102 https://doi.org/10.1371/journal.pone.0126102
31. Braine ME: Apathy a common feature in many neurological conditions: care and management. Aust J Neurosci 2014; 24:12–22, Retrieved from http://usir.salford.ac.uk/33435/
32. Manera V, Chapoulie E, Bourgeois J, et al: A feasibility study with image-based rendered virtual reality in patients with mild cognitive impairment and dementia. PLoS One 2016; 11:e0151487 https://doi.org/10.1371/journal.pone.0151487
33. Padala PR, Padala KP, Lensing SY, et al: Repetitive transcranial magnetic stimulation for apathy in mild cognitive impairment: a double-blind, randomized, sham-controlled, cross-over pilot study. Psychiatry Res 2018; 261:312–318 https://doi.org/10.1016/j.psychres.2017.12.063
34. Oguro H, Nakagawa T: Randomized trial of repetitive transcranial magnetic stimulation for apathy and depression in Parkinson's disease. J Neurol Neurophysiol 2014; 05 https://doi.org/10.4172/2155-9562.1000242
35. Sasaki N, Hara T, Yamada N, et al: The efficacy of high-frequency repetitive transcranial magnetic stimulation for improving apathy in chronic stroke patients. Eur Neurol 2017; 78:28–32 https://doi.org/10.1159/000477440
36. Ben-Sadoun G, Manera V, Alvarez J, et al: Recommendations for the design of serious games in neurodegenerative diseases. Front Aging Neurosci 2018; 10:13;doi:10.3389/fnagi.2018.00013
37. Trimarchi PD, Locatelli P, Cirilli F, et al: Elderly patients with cognitive impairment: application of a new service and organizational model supported by digital solutions. E-Health 2018 ICT, Society and Human Beings, 2018. 2018, 12
38. Massimo L, Kales HC, Kolanowski A: State of the science: apathy as a model for investigating behavioral and psychological symptoms in dementia. J Am Geriatr Soc 2018; 66(S1):S4–S12, Internet[cited 2018 Sep 25]

39. Linstone HA, Turoff M: The Delphi Method: Techniques and Applications. Reading, MA: Addison-Wesley, 1975
40. Mulin E, Leone E, Dujardin K, et al: Diagnostic criteria for apathy in clinical practice. Int J Geriatr Psychiatry 2011; 26:158–165
41. Manera V, Fabre R, Stella F, et al: A survey on the prevalence of apathy in elderly people referred to specialized memory centers. Int J Geriatr Psychiatry 2019;doi:10.1002/gps.5125, [Epub ahead of print]
42. Agüera-Ortiz L, Hernandez-Tamames JA, Martinez-Martin P, et al: Structural correlates of apathy in Alzheimer's disease: a multimodal MRI study. Int J Geriatr Psychiatry 2017; 32:922–930
43. Ang Y, Lockwood P, Apps M, et al: Distinct subtypes of apathy revealed by the Apathy Motivation Index. PLoS One 2017; 12: e0169938
44. Radakovic R, Abrahams S: Developing a new apathy measurement scale: Dimensional Apathy Scale. Psychiatry Res 2014; 219:658–663
45. Radakovic R, Stephenson L, Colville S, et al: Multidimensional apathy in ALS: validation of the Dimensional Apathy Scale. J Neurol Neurosurg Psychiatry 2016; 87:663–669
46. Banks SJ, Ng V, Jones-Gotman M: Does good + good = better? A pilot study on the effect of combining hedonically valenced smells and images. Neurosci Lett 2012; 514:1–76
47. Mishra J, Gazzaley A: Closed-loop cognition: the next frontier arrives. Trends Cogn Sci 2015; 19:242–243;doi:10.1016/j.tics.2015.03.008, 2015 May
48. Robert PH, König A, Amieva H, et al: Recommendations for the use of serious games in people with Alzheimer's disease, related disorders and frailty. Front Aging Neurosci. 2014; 6:54; doi:10.3389/fnagi.2014.00054
49. van Dalen JW, van Wanrooij LL, Moll van Charante EP, et al: Association of apathy with risk of incident dementiaa systematic review and meta-analysis. JAMA Psychiatry 2018; 75:1012–1021
50. Starkstein S, Jorge R, Misrahi R, et al: A prospective longitudinal study of apathy in Alzheimer's disease. J Neurol Neurosurg Psychiatry 2006; 77:8–11
51. Ruthirakuhan M, Herrmann N, Vieira D, et al: The roles of apathy and depression in predicting Alzheimer disease: a longitudinal analysis in older adults with mild cognitive impairment. Am J Geriatr Psychiatry 2019; 27:873–882;doi:10.1016/j.jagp.2019.02.003
52. Pedersen KF, Alves G, Brønnick K, et al: Apathy in drug-naïve patients with incident Parkinson's disease: the Norwegian ParkWest study. J Neurol 2010; 257:217–223;doi:10.1007/s00415-009-5297-x
53. Crockford C, Newton J, Lonergan K, et al: ALS-specific cognitive and behavior changes associated with advancing disease stage in ALS. Neurology 2018; 91:e1370–e1380
54. Lanctot KL, Aguera-Ortiz L, Brodaty H, et al: Apathy associated with neurocognitive disorders: recent progress and future directions. Alzheimers Dement 2017; 13:84–100
55. Starkstein S, Hayhow B: Apathy in dementia: time to standup. Am J Geriatric Psychiatry 2019; 27:406–407
56. Cohen-Mansfield J, Dakheel-Ali M, Marx MS: Engagement in persons with dementia: the concept and its measurement. Am J Geriatr Psychiatry 2009; 17:299–307;doi:10.1097/JGP.0b013e31818f3a52
57. Manera V, Ben-Sadoun G, Aalbers T, et al: Recommendations for the use of serious games in neurodegenerative disorders: 2016 Delphi Panel. Front Psychol 2017; 8:1243;doi:10.3389/fpsyg.2017.012