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THÈSE DE DOCTORAT

Remédiation du déficit de reconnaissance des émotions faciales chez les personnes atteintes de Maladie d'Alzheimer : quels bénéfices pour le patient et son aidant à court et à long terme ?

*Remediation of facial emotion recognition impairment in people with Alzheimer's disease:
what short and long-term benefits for the patient and the family caregiver?*

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Laboratoire d'Anthropologie et de Psychologie Cliniques, Cognitives et Sociales (LAPCOS)

**Présentée en vue de l'obtention
du grade de docteur en Psychologie
d'Université Côte d'Azur**

Dirigée par : Pr Edith Galy

Co-dirigée par : Dr Kévin Polet

Co-encadrée par : Dr Sandrine Louchart
de La Chapelle

Soutenue le : 20 octobre 2023

Devant le jury, composé de :

Sylvane Faure, Professeur, Université Côte
d'Azur

Fabrice Guillaume, Professeur, Université Aix-
Marseille

Hélène Brissart, HDR, CHU de Nancy

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Remédiation du déficit de reconnaissance des émotions faciales
chez les personnes atteintes de Maladie d'Alzheimer :
quels bénéfices pour le patient et son aidant à court et à long terme ?

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La reconnaissance des émotions faciales (REF) est altérée dans les maladies neurodégénératives (MND). Ce déficit est lié à une perturbation des stratégies d'observation des visages émotionnels conjointement à une augmentation des symptômes comportementaux et psychologiques de la démence (SCPD), source majeure du fardeau des aidants. L'étude préliminaire de Polet et al., 2021, menée auprès de personnes atteintes de maladie d'Alzheimer (MA) a montré qu'un programme de remédiation cognitive de la REF permettait d'améliorer la REF suite à une modification des patterns d'observation des visages. En parallèle, une diminution des SCPD et du fardeau de l'aidant était observé. Ces effets se maintiennent un mois après l'intervention.

Ces résultats semblent encourageants afin de prendre en charge la personne atteinte de MA et son aidant. Mais, ils ont été obtenus auprès de petits échantillons et par le biais de visages expressifs statiques, peu écologiques. Bien que des résultats positifs aient été décrits un mois post remédiation, existe-t-il des bénéfices à plus long terme ? De plus, à notre connaissance, aucune étude n'a permis de désigner quelle approche était la plus efficace pour améliorer les capacités de REF dans les MND.

Pour répondre à ces problématiques, cette thèse s'appuie sur trois études : (1) une revue systématique de la littérature et une méta-analyse qui avaient pour objectif de répertorier et de comparer l'efficacité des différentes interventions visant à améliorer la REF dans les MND ; (2) une étude randomisée contrôlée en simple aveugle dont l'objectif était de confirmer les résultats préliminaires, auprès d'un échantillon plus conséquent et en ajoutant un matériel plus écologique d'évaluation de la REF en utilisant des visages expressifs dynamiques ; (3) une étude évaluant l'impact à long terme (>2 ans) de cette remédiation cognitive de la REF auprès des participants issus de l'étude préliminaire.

Nous avons montré que trois types d'approches amélioraient la REF dans les MND : l'approche pharmacologique, la neurostimulation et la remédiation cognitive (la plus efficace). La seconde étude a confirmé les résultats préliminaires, à savoir une amélioration de la REF statiques suite à la remédiation, et a mis en évidence une moindre amélioration de la REF dynamiques dans la MA. Cette amélioration était conjointe à une modification des stratégies d'observation des visages expressifs statiques. Pour les visages dynamiques, la remédiation a permis de maintenir une exploration visuelle optimale des visages



expressifs, alors qu'elle se dégradait au sein du groupe contrôle, témoignant d'une altération progressive de la saillance émotionnelle. En parallèle, une diminution des SCPD et du fardeau de l'aidant pour le groupe ayant eu la remédiation étaient observée. Ces effets se maintenaient un mois après l'intervention. Enfin, la troisième étude a montré qu'il n'y avait pas de maintien des performances de REF à 2 ans. Consécutivement, un haut niveau de SCPD et de fardeau de l'aidant était retrouvé dans le groupe ayant bénéficié de la remédiation. Néanmoins, aucun participant de ce groupe n'était institutionnalisé au moment de ce re-test, l'hypothèse étant que ces personnes présentaient moins de SCPD, permettant ainsi un maintien à domicile.

En conclusion, la REF peut être améliorée dans les MND, ces bénéfices pouvant perdurer dans le temps malgré le cours évolutif de ces maladies. Compte tenu de l'influence de ce type de prise en charge sur les SCPD, et par conséquent sur le fardeau de l'aidant, il serait utile d'étudier les possibilités d'optimisation de ces interventions sur les mécanismes d'orientation de l'attention sur les zones clés du visage. Il serait aussi intéressant de combiner les différentes approches identifiées afin d'étudier une éventuelle potentialisation de leurs effets. Une étude longitudinale croisant ces approches pourrait permettre d'observer leurs effets sur l'apparition des SCPD dans les MND.

Mots clés :

Reconnaissance des émotions faciales, Maladies neurodégénératives, Remédiation cognitive, Eye-Tracking, Symptômes Comportementaux et Psychologiques de la Démence, Fardeau de l'aidant



Facial emotion recognition (FER) ability is impaired in neurodegenerative diseases (NDD). This impairment is linked to an atypical visual scanning on the key areas of the faces expressing an emotion and associated with an increase in behavioral and psychological symptoms of dementia (BPSD), the latter are major factor of caregiver burden. A preliminary study, by Polet et al., 2021, in people with Alzheimer's disease (AD) showed FER performances were improved following a cognitive remediation program of FER. Improvement was due to modification of eye-gaze strategies during FER. At the same time, a decrease in BPSD and the family caregiver burden was observed. Finally, these effects were maintained one month after the intervention.

These results seem to be an interesting avenue for the care of both AD individuals and their caregivers. Nevertheless, these results were obtained from small samples size and through non-ecological materials (static expressive faces). Although positive results were described one month after remediation, we wondered if there were long-term benefits? Moreover, to our knowledge, no study has identified which approach was the most effective in improving FER abilities in NDD.

To answer these issues, this thesis is based on three studies: (1) a systematic review of the literature and a meta-analysis which aimed to identify and compare the effectiveness of different interventions targeted FER abilities in NDD; (2) a randomized controlled single-blinded study whose objective was to confirm the preliminary results, with a larger sample size of people with AD and by adding a more ecologic assessment for FER abilities through the use of dynamic expressive faces; (3) a study aimed to assess the long-term impact (>2 years) of this cognitive remediation of FER on participants from the preliminary study.

We highlighted that three types of approaches allow to improve the FER ability in NDD: the pharmacological approach, neurostimulation, and cognitive remediation (the most



efficient). Our second study confirmed the preliminary results, namely a FER ability improvement for static faces after FER remediation, and highlighted a mild improvement in FER ability for dynamic faces in AD. This beneficial effect for static faces was combined with a modification of eye-gaze strategies for static expressive faces. For dynamic faces, the FER remediation allowed to maintain an optimal visual exploration of the expressive faces, whereas within the control group this exploration was modified, testifying to a progressive degradation of the emotional salience. In parallel, a reduction in BPSD and the family caregiver burden level for the group who received FER remediation was observed. These effects were maintained one month after the intervention. Finally, our third study showed that there was no maintenance of FER performance at 2 years. Consecutively, a high level of BPSD and family caregiver burden was found in participants who received remediation. Nevertheless, no participant in this group was institutionalized at the time of this re-test, we hypothesized that these people had less BPSD, thus allowing to continue in home care.

This thesis shows that FER ability can be improved in NDD as in AD and that these benefits can persist over time despite the evolutionary course of these diseases. Given the influence of this type of remediation on BPSD, and consequently on the family caregiver burden, it would be useful to study the possibilities of optimizing these interventions on the mechanisms of attentional orientation to the key areas of the face. It would also be interesting to combine the cognitive approach with pharmacological and neurostimulation approaches to study a possible potentiation of their effects. A longitudinal study combining these types of approaches could make it possible to observe their effects on the appearance of BPSD in NDD which BPSD are often at the forefront of the clinical presentation.

Keywords:

Facial emotion recognition, Neurodegenerative diseases, Cognitive Remediation, Eye-Tracking, Behavioral and Psychological Symptoms of Dementia, Caregiver Burden





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- *Mais de rien Naz !*

- *Non, j'insiste, merci beaucoup Naz !*

- *Bon, ok ! j'accepte !*





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"Si un jour mes propos vont à l'encontre de la science, choisissez la science."

*"Biz her şeyi gençliğe bırakacağız... Geleceğin ümidi, ışıklı çiçekleri onlardır.
Bütün ümidim gençliktedir"*

"Nous laisserons tout aux mains de la jeunesse...L'espoir d'un avenir, les fleurs lumineuses, sont la jeunesse. Je mets tout mon espoir en la jeunesse"





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to Mustafa Kemal Atatürk

to my mom



Abbreviations

AD: Alzheimer's Disease.

APO: continuous subcutaneous infusion of apomorphine

BPSD: Behavioral and Psychological Symptoms of Dementia.

bvFTD: behavioral variant of Frontotemporal Dementia.

CATS: Comprehension affects the testing system.

CST: Cognitive Stimulation Therapy.

DRT: Dopamine Replacement Therapy.

FER: Facial Emotion Recognition.

HC: Healthy Control.

HYC: Healthy Young Controls.

HD: Huntington's disease.

CI: Confidence Interval.

KDEF: Karolinska-directed emotional faces.

METT: MicroExpression training tool.

MMSE: Mini-Mental State Examination.

MA : Maladie d'Alzheimer

MH : Maladie de Huntington

MP : Maladie de Parkinson

NPI : Neuropsychiatric Inventory

NDD: Neurodegenerative Disease.

Ni: sample of the intervention group

Nc: sample of the control group.



Nfs: fail-safe number of Rosenthal's.

ODT: Optimal Drug Therapy.

PD: Parkinson's Disease.

PPA: Primary Progressive Aphasia.

REF : Reconnaissance des Emotions Faciales

RE : Random Effects.

RI : Région d'Intérêt

ROI : Region Of Interest

SCPD : Symptômes Comportementaux et Psychologiques de la Démence

SSRI: Selective Serotonin Reuptake Inhibitor.

STN: Subthalamic Nucleus.

STN-DBS: Subthalamic Nucleus Deep-Brain Stimulation.

STS: Superior Temporal Sulcus

TAR: Training of Affect Recognition.

TASIT: Awareness of Social Inference Test.

tDCS: transcranial Direct Current Stimulation

TMS: Transcranial Magnetic Stimulation

VPP: Vertex Positive Potential



Articles

Mirzai, N., Galy, E., Louchart de la Chapelle, S., Hesse, S., Morisot, A., Pesce, A., Polet, K. (soumis le 18/08/2023, Journal of Geriatric Psychiatry and Neurology). Facial emotion recognition ability can be improved in Alzheimer's disease: A randomized-controlled, single-blinded study.

Mirzai, N., Polet, K., Morisot, A., Hesse, S., Pesce, A., de la Chapelle, S. L., & Iakimova, G. (2023). Can the Ability to Recognize Facial Emotions in Individuals With Neurodegenerative Disease be Improved? A Systematic Review and Meta-analysis. *Cognitive and Behavioral Neurology*, 10-1097.



Mirzai, N., Polet, K., Louchart de la Chapelle, S., Hesse, S., Morisot, A., Pesce, A., & Galy, E. (2023). Effets à long terme d'une remédiation de la reconnaissance des émotions faciales et de ses conséquences cliniques dans la maladie d'Alzheimer. *NPG Neurologie - Psychiatrie - Gériatrie*. <https://doi.org/10.1016/j.npg.2023.03.006>



Polet, K., Mirzai, N., Hesse, S., Morisot, A., Kullmann, B., Louchart de la Chapelle, S., Pesce, A., & Iakimova, G. (2021). Remédiation de la reconnaissance des émotions faciales dans la maladie d'Alzheimer et effets sur les stratégies d'observation, les troubles du comportement et le fardeau de l'aidant. *Neurologie Psychiatrie Gériatrie*, 21(121), 25- 36. <https://doi.org/10.1016/j.npg.2020.08.003>.



Oral communications

Mirzai, N. (2022, Novembre). « Remédiation des déficits en reconnaissance des émotions faciales chez les personnes avec une Maladie d'Alzheimer : quels bénéfices pour le patient et son aidant à court et à long terme ? »[communication lors du remise du prix Chaffoteaux]. 42ème Journées Annuelles de la Société Française de Gériatrie et Gérontologie (JASFGG), Paris, France



Mirzai, N. (2022, Novembre). « Maladies Neurodégénératives et reconnaissance des émotions: Remédiations de la REF: aide aux aidants ? » [communication]. 42eme Journées Annuees de la Société Française de Gériatrie et Gérontologie (JASFGG), Paris, France

Mirzai, N. (2022, Novembre). « Réhabilitation de la reconnaissance des émotions dans la Maladie d'Alzheimer et étude des conséquences sur la stratégie du regard, les troubles du comportement et le fardeau des aidants familiaux : effets à court, à moyen et à long terme »[communication]. 42eme Journées Annuelles de la Société Française de Gériatrie et Gérontologie (JASFGG), Paris, France.

Posters

Mirzai, N., Polet K., Louchart de la Chapelle, S., Hesse, S., Morisot, A., Pesce, A., Iakimova., G. (2022, Septembre). Rehabilitation of facial emotion recognition in Alzheimer's disease and study of the consequences on behavioural disorders and family caregiver's burden: a long-term follow-up study [affiche]. 18th International Congress of European Geriatric Medicine Society, Londres, Angleterre.



Mirzai, N., Polet, K., Hesse, S., Morisot, A., Iakimova, G., Pesce, A., Louchart de la Chapelle, S. (2021, Septembre) Prises en charges du déficit de la reconnaissance des émotions faciales dans les maladies neurodégénératives : revue systématique de la littérature et méta-analyse.CFP [affiche] Journées de Neurologie de Langue Française, Strasbourg, France.



Polet, K, Mirzai N, Hesse S, Morisot A, Iakimova G, Louchart de la Chapelle S, Pesce A., Réhabilitation de la reconnaissance des émotions faciales dans la Maladie d'Alzheimer et conséquences sur l'aidant familial [affiche]. Réunion Francophone sur la Maladie d'Alzheimer & Syndrome Apparentés, Marseille, France



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La Fondation de France et la Société Française de Gériatrie et de Gérologies (SFGG) ont remis la 7^e édition prix Lucie & Edouard Chaffoteaux pour soutenir les travaux de recherche de cette thèse. Ce prix récompense les recherches à l'origine d'une avancée significative en gériatrie et gérologie. La remise de prix a eu lieu le 7 novembre 2022 durant les 42es Journées Annuelles de la SFGG.



The Foundation of France and the French Society of Geriatrics and Gerontology (SFGG) awarded the 7th edition of the Lucie & Edouard Chaffoteaux Prize to support the research of this thesis. This award recognizes research leading to significant progress in geriatrics and gerontology. The award ceremony took place on November 7, 2022, during the 42nd Annual Days of the SFGG.





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GENERAL INTRODUCTION

Introduction

The World Health Organization predicts that the number of individuals affected by Alzheimer's Disease (AD) will rise as the world's population ages, with an estimated 115.4 million people affected by 2050 (Organization, 2021). In France, more than one million people are affected by a neurodegenerative disease (Wanneveich et al., 2018), the most common being AD, which accounts for 70% of cases (Ramaroson et al., 2003; Helmer et al., 2006).



Facial emotion recognition (FER) is a crucial aspect of social cognition and plays a significant role in daily social interactions. However, this ability is often impaired in neurodegenerative diseases (NDD) like AD (Christidi et al., 2018).



Poor FER ability resulting in interpersonal difficulties (Shimokawa et al., 2001) and is negatively correlated with behavioral and psychological symptoms of dementia (BPSD) (Kempnich et al., 2018), which are a major factor in family caregiver burden (Martinez et al., 2018) and a source of early institutionalization (Chan et al., 2013). In this context, caregivers may experience social disconnection and isolation when their care recipients cannot recognize emotions and respond appropriately, leading to increased caregiver burden (Brown et al., 2018).



Impairment of FER in NDD is associated with atypical patterns of visual scanning of faces expressing an emotion (Polet et al., 2022). Studies showed shorter exploration duration in the scanning of emotional faces and fewer fixations on the eye region in AD (Ogrocki et al., 2000). Following the rehabilitation of FER, patients with AD had improved FER performance and increased observation of the upper part of expressive faces (Polet et al., 2021), confirming that FER ability, BPSD and gaze strategies are linked (Polet et al., 2022).



Consequently, addressing FER impairment in individuals with NDD could be a beneficial approach to alleviate BPSD, ease the burden on family caregivers, and potentially delay institutionalization.

However, it should be noted that these results were based on small sample sizes and non-ecological materials, specifically static expressive faces. Although we observed positive results a month after the remediation, we are curious about the long-term benefits. To date, there was a lack of studies determining the most effective method for enhancing FER skills in individuals with NDD.

To establish our hypothesis and showcase the research we conducted, this thesis is structured into four distinct parts.

The first part consists of a review of the literature related to the theoretical context of this thesis work. **Chapter 1** will provide a detailed explanation of FER ability. Additionally, we will discuss how ageing and NDD can affect this ability, and the repercussions of FER impairment on behavior, caregiver burden and institutionalization. **Chapter 2** will focus on the eye gaze strategies during the visual exploration of emotional faces, especially in normal ageing and NDD. **Chapter 3** will present FER targeted cognitive remediation programs and their application to improve this ability in AD.

In the second part, we will provide a summary of this literature review and will indicate the objectives of this thesis (**Chapter 4**).

The third part will be devoted to the experimental contributions of this thesis. The first study, named “Systematic Review and Meta-analysis” (**Chapter 5, Mirzai et al., 2023b**), identifies and compares the effectiveness of different interventions to improve FER in NDD and explores the duration of their effects and their possible impacts on BPSD and caregiver burden. The second study, named “EYE-TAR (AD+)” (**Chapter 6, submitted**), in line of the preliminary results published (see Appendix 1 Polet et al., 2021), investigates the remediation of FER ability

in AD and the triple interaction between FER impairment, atypical gaze strategy, and BPSD in a larger sample and by using more ecological material: dynamic FER assessment. And, the third study, named “EYE-TAR (MA) Follow up” (**Chapter 7, Mirzai et al., 2023a**) explores the long-term impact of the FER remediation program by assessing at 2 years the participants from the preliminary study (Polet et al., 2021).

To conclude the thesis, **in the fourth part**, we will discuss all the results of the studies, the clinical implications and the limitations. And we will propose new perspectives based on this thesis work for clinical practice.

PART I: THEORETICAL FRAMEWORK

CHAPTER I: FACIAL EMOTION RECOGNITION

1. Definitions

1.1. Social cognition

Social cognition refers to the abilities by which we perceive, interpret and process social information about ourselves and others (Bertoux, 2022). It allows the individual to understand and interact with others by adopting appropriate behaviours (Adolphs, 2009). Social cognition is essential for constructing and maintaining interpersonal interactions (Zhu et al., 2018). A systematic mapping review Fernández-Sotos et al., (2019) showed that social cognition is a research area that has generated growing interest in the last decade, particularly in neurological clinics where the assessment of social cognition abilities provides support for functional assessment and differential diagnosis (Bertoux, 2022).

Social cognition relies on many low and high-level “social cognitive functions” (Bertoux, 2022). Among these “social cognitive functions”, we find:

- **Theory of Mind:** the ability to infer the mental states of others (their knowledge, intentions, beliefs, or emotions) and to identify them as different from our own (Frith & Frith, 2006; Saxe et al., 2004). This ability is subdivided into two components: a cognitive Theory of Mind (inferences from what a person is thinking) and an affective Theory of Mind (inferences from what a person is feeling) (Samson, 2012; Sebastian et al., 2012; Shamay-Tsoory, 2015)

- **Empathy:** the ability to share and feel the emotions of others and to produce inferences about one’s emotional state to understand it (Decety & Lamm, 2006). This ability allows us to understand others’ thoughts and feelings (Decety & Jackson, 2004; Decety & Lamm, 2006). It is a complex ability also subdivided into two components: cognitive empathy allowing the inference and understanding of the emotions of others (similar to the affective Theory of Mind) (Bertoux, 2016), and an affective component consisting of affective response to the inferred affect (Batson, 2009; Sebastian et al., 2012; Shamay-Tsoory, 2015).

- **Emotional functioning:** it is a set of specialized skills referring to emotions' experience, expression, perception, and conceptualization. Milojevich et al., (2021) propose a classification by distinguishing five specific domains. (1) Emotion expression refers to the behavioural manifestations of expressing an emotion using the face, body and/or voice (Russell et al., 2003). (2) Emotion perception, also called "emotion recognition", is the ability to identify the emotions expressed by others based on their facial, vocal and/or bodily expressions and contextual cues (Pollak & Sinha, 2002). Especially, facial emotion recognition (FER) ability is described below in section b of this chapter. (3) Emotion knowledge refers to the specific semantic knowledge of each individual about emotions and their functioning (Izard et al., 2001). This knowledge of emotions allows us to access complex emotions and relate them to given contexts. Emotional reasoning, therefore, becomes more elaborate and allows, for example, being able to question the emotional feelings of a person, or to control our reactions, depending on the context. (4) Emotion reactivity refers to the sensitivity, intensity, and persistence of an emotional experience in response to a wide range of stimuli (Milojevich et al., 2021). (5) Emotion regulation is defined by Thompson (1994) as a field consisting of the internal and external processes involved in initiating, sustaining, and modulating the occurrence, intensity, and expression of emotions.

1.2. Facial emotion recognition

1.2.1. Facial emotion expression

According to Darwin, (1872) emotional expressions would have provided an adaptative advantage during evolution and would fulfil a crucial role in communication. Emotions can be defined as states of relatively short duration that lead to a motor (leakage, facial/body expression etc.), physiological (heart rate, sweating, breathing, etc.) and cognitive (reorientation of attention, feeling of pleasure /unpleasure) responses (Frijda, 2000). Emotions are above all intentions to act (Frijda, 2007): for example, a cheerful face can indicate an

opportunity for social interaction, while an expression of anger can signal a threat (Levenson et al., 2017; Schmidt & Cohn, 2001) that makes to decide whom to approach and whom to avoid (Shdo et al., 2022).

Ekman, (1992) identified six primary and universal facial expressions (Fig. 1): **joy**, **anger**, **disgust**, **surprise**, **fear**, and **sadness** that present innately in all individuals regardless of their culture. And he distinguished secondary emotions which are more complex and culturally acquired (Ekman et al., 1969, 1978; Ekman & Friesen., 1976).

Each facial expression corresponds to a specific configuration of contraction/relaxation of the facial muscles. These are thus coded within the Facial Action Configuration System (FACS), in which each facial expression corresponds to a combination of *action units*, the latter indicating the state of each muscle of the face (Fig. 1) (Ekman & Friesen, 1978). For example, as illustrated in Fig. 1 photo F, the surprise is expressed by a combination of action units involving movements of the jaw, lips, and eyebrows (Ekman & Rosenberg, 2005).

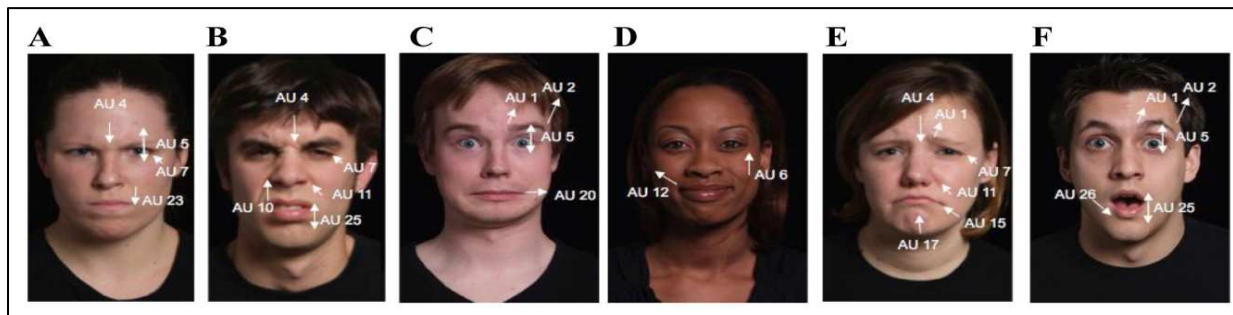


Fig. 1: Facial Action Coding System for six primary emotions (Barrett et al., 2019). **A.** anger. **B.** disgust. **C.** fear. **D.** joy. **E.** sadness. **F.** surprise. AU, action units.

The so-called secondary or complex emotions, such as shame, jealousy, or admiration, would result from the combination of primary emotions and would be dependent on culture and experience (Becker-Asano & Wachsmuth, 2008; Damasio, 1994; Nugier, 2009).

1.3. Factors influencing the recognition of facial emotions

Although the ability to recognize facial expressions is innate and universal, there is a great performance heterogeneity between individuals. The progression of FER performances is

constant during childhood and accelerates under the influence of puberty before stabilizing (Lawrence et al., 2015) and then deteriorating with ageing (cf. section 2 of this chapter). There are many factors influencing FER ability such as,

- 1. Sex:** Several studies have shown that women have a better FER performance compared to men (Gonçalves et al., 2018; Olderbak et al., 2019; Quesque et al., 2020) more precisely, women are better at recognizing fear and worse at recognizing disgust compared to men (Gonçalves et al., 2018).
- 2. Ethnicity and culture:** In general, individuals are better at recognizing the emotions expressed by individuals of their ethnic group (Elfenbein & Ambady, 2002). In addition to ethnicity, cultures shape the way of expressing and therefore FER (Lim, 2016; Schouten et al., 2020). A study conducted with a large population of healthy subjects from 12 different countries showed 21% of the performance variance of FER (Quesque et al., 2020). They showed that English participants had the best overall scores, while Italian and Spanish participants had the worst and this was attributable to nationality: in general, joy was easier to recognize whereas recognition of fear and disgust was influenced by culture.
- 3. The education level:** Some studies have shown a positive correlation between educational level and FER performances (Demenescu et al., 2014; Kessels et al., 2014a; Trauffer et al., 2013) especially for fear and disgust recognition (Gonçalves et al., 2018; Trauffer et al., 2013) while others found a correlation between FER performances and sex/culture rather than the education level (Quesque et al., 2020)
- 4. Wearing a face mask:** The COVID-19 pandemic has resulted in the wearing of a face mask within the general population with potential consequences on social interactions knowing that the mask covers 2/3 of the face including the mouth and nose (Kleiser et al., 2022). Numerous studies have thus highlighted a deleterious effect of wearing a face

mask on the FER ability (Cooper et al., 2022; Gori et al., 2021; Grahlow et al., 2022; Henke et al., 2022; McCrackin et al., 2021; Rinck et al., 2022; Thomas et al., 2022; Wong & Estudillo, 2022), especially for the recognition of disgust, sadness, joy, anger and fear (McCrackin et al., 2021).

1.3.1. Brain structures involved in facial emotion recognition

FER results from the activation of several key brain structures distributed throughout the brain (Frith, 2007). Among these key brain structures, the somatosensory cortex, which has a global role in the ability to understand the emotional meaning of facial expressions (Adolphs et al., 2000), and the superior temporal sulcus, the orbitofrontal cortex, basal ganglia, insula, the temporal lobes, in particular, the amygdala and the fusiform gyrus have a role in FER (Adolphs, 2002; Adolphs et al., 1999; Davis & Whalen, 2001; Mende-Siedlecki et al., 2013; Sabatinelli et al., 2011; Sapey-Triomphe et al., 2015; Vuilleumier & Pourtois, 2007; Winston et al., 2003). Below, we detail especially the most involved structures in recognizing each primary emotion. **Fear**, the most studied facial expression, is mainly related to the activation of the amygdala (Adolphs et al., 1994; Breiter et al., 1996; Calder et al., 2001; Morris et al., 1996; Whalen, 1998).

Anger, in addition to the amygdala (Fischer et al., 2005; Morris et al., 1998), the cingulate cortex and especially the orbitofrontal cortex are the structures the most solicited to recognize this emotion (Blair & Cipolotti, 2000; Blair et al., 1999; Fine & Blair, 2000; Iidaka et al., 2001; Murphy et al., 2003).

Disgust is mostly linked to the activation of the basal ganglia and the insula (Calder et al., 2001; Woolley et al., 2015)

Joy is mainly linked to the activation of the basal ganglia and the amygdala structures (Breiter et al., 1996; Phan et al., 2002; Whalen, 1998). The orbitofrontal cortex is also involved (Goutte & Ergis, 2011).

Sadness recognition is most linked to the right amygdala and temporal pole (Blair et al., 1999) and the subgenual cingulate cortex activation. (Phan et al., 2002)

Surprise is linked to a particular role of the parahippocampal gyrus (Schroeder et al., 2004)

These cerebral structures involved in FER are interconnected by numerous fasciculus of white matter (Fig. 2). First, two long-distance association fasciculus connect visual structures to emotional structures: the inferior longitudinal fasciculus and the frontal-occipital fasciculus. They have a major role in allowing the different structures of the network to communicate and realize FER (Unger et al., 2016), especially for recognizing fear, anger and sadness (Genova et al., 2015; Philippi et al., 2009). The inferior longitudinal fasciculus connects the occipital cortex to the anterior temporal pole, which is an important brain networks hub involved in social cognition abilities, from which the uncinate fasciculus connects the temporal lobe to the frontal lobe through the amygdala, the insula, and the orbitofrontal cortex (Coad et al., 2020). The uncinate fasciculus is important in regulating FER processing (Coad et al., 2020; Nguyen et al., 2017). Then, another long-association fasciculus, the superior longitudinal fasciculus, relates to the temporal cortex and the frontal cortex via the parietal lobe (Nakajima et al., 2020). The superior longitudinal fasciculus is involved in emotion recognition, whether facial (Crespi et al., 2014; Philippi et al., 2009; Radoeva et al., 2012), conveyed by a story (Crespi et al., 2014) or by a voice (Ethofer et al., 2012, 2013). Finally, an afferent pathway relating the pulvinar to the amygdala would facilitate fear recognition (McFadyen et al., 2019).

The advent of diffusion tractography permitted the study of the association of white matter fibers between brain areas. Hence, the modular design of social cognition (based on key brain areas) gave way to circuits and networks modelisation, called the “social brain networks”. (Kennedy & Adolphs, 2012). The “social brain networks” (Fig.2) lean in three large networks: the “face perception network” implicated in face perception (Duchaine & Yovel, 2015; Gobbini

& Haxby, 2007; Haxby et al., 2000), the “mirror neuron system” implying mirror neurons (Gallese, 2007), and the “mentalizing network” known as the network of the theory of mind.

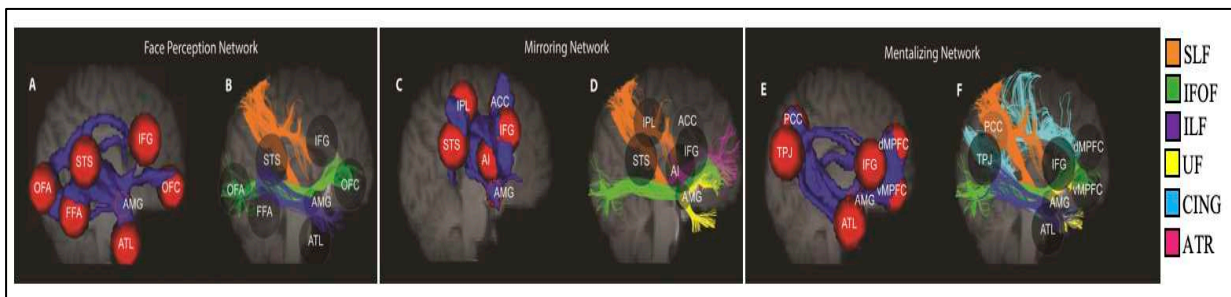


Fig. 2. White matter pathways of social brain (Wang et al., 2018). ACC, anterior cingulate cortex; AI, anterior insula, AMG, amygdala; ATL, anterior temporal lobe; ATR, anterior thalamic radiation; CING, cingulum bundle; dmPFC, dorsolateral prefrontal cortex; FFA, fusiform face area; IFG, inferior frontal gyrus; IPL, inferior parietal lobule, OFA, occipital face area; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; SLF, superior longitudinal fasciculus; STS, superior temporal sulcus; TPJ, temporo-parietal junction; IFOF, inferior frontal occipital fasciculus; ILF, inferior longitudinal fasciculus; UF, uncinata fasciculus

1.3.2. Cognitive functions involved in facial emotion recognition.

FER ability is one of social cognition abilities (Pinkham et al., 2014). And the latter refers to any cognitive processing, such as perception, reasoning, memory, attention, motivation, and decision-making, which appears to be relatively specialized for the social domain (Christidi et al., 2018). Not only the language (Bertoux, 2022) but episodic working memories and executive functions are implicated in the well-functioning of social cognition (Stone & Gerrans, 2006). Some studies have found a correlation between cognitive abilities and FER (Granato et al., 2014; Murphy & Lilienfeld, 2019; Suzuki & Akiyama, 2013); more precisely, information processing speed, executive functions, attention, working memory and visuo-perceptual abilities are related to FER (Circelli et al., 2013; García-Rodríguez et al., 2012; Horning et al., 2012; Lambrecht et al., 2012; Murphy & Lilienfeld, 2019; van Hooren et al., 2008). Recent studies have also indicated a role of semantic knowledge in FER ability (Bertoux et al., 2020; 2022).

1.4. Assessment of facial emotion ability

FER assessments are traditionally based on photographs to assess static FER ability or on videos to assess dynamic FER ability.

1.4.1. Static facial emotion recognition assessment

The Ekman's Faces Test (Ekman & Friesen, 1976) is the most used test, according to the review by Ferreira et al., (2021). It identifies and faces expressing the six primary emotions and the neutral condition by 77 black and white photographs of men's and women's faces. The NimStim set of facial expressions (Tottenham et al., 2009) is a large dataset comprising 672 photographs by 43 actors (18 female, 25 male) aged 21 to 30, including eight emotional expressions: neutral, angry, disgusted, surprised, sad, calm, happy, and scared. Open and closed-mouth versions were provided for all emotional expressions except for surprise and joy. Other assessment types are as follows: Affect GARDIOR (García-Casal, Vanova, et al., 2017), the Karolinska-directed emotional faces (Lundqvist and Öhman, 1998), Comprehension Affect Testing System (Froming et al., 2006), Florida Affect Battery (Bowers et al., 1989).

1.4.2. Dynamic facial emotion recognition assessment

The Amsterdam Dynamic Facial Expression Set (ADFES) (van der Schalk et al., 2011) is the first standardized test concerning videos (in color), created based on Ekman's FACS (1976), allowing to assessment of FER ability more ecologically. It consists of dynamic facial expressions, displayed by 22 models (10 females, 12 males, both Northern European and Mediterranean), with active head rotation to clarify the directedness of each facial expression, all for nine emotions: the six "basic" emotions (joy, anger, fear, sadness, surprise, disgust), as well as contempt, pride, and embarrassment. Each video begins with a neutral face and ends with the peak intensity of emotion. There is also a subtest (the Emotion Evaluation Test) of the Awareness of Social Inference Test (McDonald et al., 2003).

2. Facial emotion recognition ability in normal ageing

The ability to interpret the emotional states of others is not constant throughout life (Brosigle & Weisman, 1995; Calder et al., 2003; McDowell et al., 1994). A better FER performance was observed among young people aged 15 to 30, with a gradual decline after 30 years, and better performance in women than men throughout their life (Olderbak et al., 2019). Compared to young people, older people have difficulty in identifying negative emotions such as anger, sadness, and fear (Grainger et al., 2015; Hayes et al., 2020; Ruffman et al., 2008; Virtanen et al., 2017), while recognition of joy remains preserved (Horning et al., 2012; Isaacowitz et al., 2007; Kessels et al., 2014; Ruffman et al., 2008; West et al., 2012). There is conflicting evidence for disgust recognition, which is preserved through ages for some authors (Calder et al., 2003; Hayes et al., 2020; Suzuki et al., 2007; Wong et al., 2005), and altered for others (Carvalho et al., 2014; Demenescu et al., 2014; Guarnera et al., 2018). Regarding surprise, there seems to be degradation during ageing (Abbruzzese et al., 2019).

The above results are concluded for static mode presentation with photographs. When it comes to dynamic mode presentation (videos of faces), some studies concluded that older people have difficulty (Ruffman et al., 2009), while other studies concluded that, compared to static, dynamic presentation improved FER performances for young and older adults equally, except for low-intensity emotional faces, where middle-aged and older adults had a significant improvement over younger adults (Grainger et al., 2015). Static FER impairment concerns negative emotions when expressed with high intensity and concerns all emotions (surprise especially) when expressed with low intensity (Hayes et al., 2020). This progressive deterioration through age could be explained by three reasons (Ebner et al., 2012) listed below.

Structural changes: The ventromedial, ventrolateral and dorsolateral prefrontal cortices, anterior cingulate cortex, insula, and thalamus were found to show significant age-related volume losses (Petit-Taboué et al., 1998; Takahashi et al., 2011) which are structures involved

in FER ability (Adolphs, 2002; Grimm et al., 2006; Phillips et al., 2003). Additionally, changes were found in the intra-network functional connectivity of visual and sensory-motor networks involved in internally directed cognitive activities (the default mode network) and in externally directed higher-order cognitive activities (the central executive network) also implicated in FER (Bressler & Menon, 2010; Chiong et al., 2013; Touroutoglou et al., 2015; Uddin et al., 2010)

Visual scanning modifications *will be defined in Chapter 2.*

Deterioration of cognitive functions: Ample evidence shows an age-related decline in executive functions and processing speed (Circelli et al., 2013; Hedden & Gabrieli, 2004; Phillips et al., 2010; Raz et al., 2011). Also, studies have pointed out that in ageing, there are both differences in attentional and perceptual ability contributing to an impairment in FER (Birmingham et al., 2018). And that the perception of facial expressions is linked to the ability to perceive faces (face perception), to remember faces (face memory), to remember faces with emotional expressions (emotion memory) and to the overall cognitive efficiency (Hildebrandt et al., 2015).

3. Facial emotion recognition ability in Alzheimer's disease and related syndromes

Numerous studies suggest that processes of social cognition abilities such as the Theory of Mind, empathy, and FER are associated with the activation of a complex neural network involving white matter regions (Wang & Olson, 2018) and several cortical regions such as the prefrontal cortex, paracingulate cortex, temporoparietal junctions, amygdala, and hippocampus (Christidi et al., 2018; García et al., 2018; Mar, 2011; Skuse & Gallagher, 2011). Therefore, neurodegenerative diseases that disturb this neurobiological system could lead to social cognition impairment (Duclos et al., 2018).

3.1. Alzheimer's Disease

Alzheimer's Disease (AD) is the most frequent neurodegenerative disease and is identified as the first cause of cognitive disorders (Frisoni et al., 2010). All dementias combined; it represents 70% of cases and it is the first cause of dementia after 65 years (Ramaroson et al., 2003; Helmer et al., 2006). AD is characterized by the abnormal accumulation of two proteins: tau and amyloid. The beta-amyloid protein aggregates in plaques causing neuronal suffering, in parallel there is hyperphosphorylation of the tau protein causing neurofibrillary degeneration resulting in neuronal death (Hardy & Selkoe, 2002). Classic form of AD manifests by progressive episodic memory impairment which is related to the entorhinal cortex, hippocampus, and external temporal associative regions atrophy (Bediou et al., 2009; Braak & Braak, 1996).

Impairment of FER ability is a debate subject in AD. For some authors this ability is impaired (Bediou et al., 2009; Hargrave et al., 2002; Henry et al., 2009; Satler et al., 2009; Spoletini et al., 2008; Torres et al., 2015; Torres Mendonça De Melo Fádel et al., 2018), even from the prodromal stage of the pathology (Teng et al., 2007). While other authors stipulate that it is preserved at the beginning stage of the disease (Bertoux et al., 2015) or significantly altered at a moderate stage of the disease (Hargrave et al., 2002). The dysfunction of temporoparietal regions would be the principal cause of FER impairment in this disease (Cadieux & Greve, 1997; Ossenkoppele et al., 2015; Teng et al., 2007). The impairment concerns negative emotions such as fear, anger, disgust, and sadness rather than joy recognition which is preserved (Fernández-Ríos et al., 2021; Park et al., 2017; Torres Mendonça De Melo Fádel et al., 2018). Especially an alteration of the uncinate fasciculus connecting the prefrontal cortex to the anterior temporal cortex could be a reason for the negative FER impairment (Takahashi et al., 2020). Another debate is whether the impairment of emotion processing is a separate entity (Bediou et al., 2009; Klein-Koerkamp et al., 2012) or a consequence of global

cognitive deterioration (Albert et al., 1991; Bucks & Radford, 2004; Cadieux & Greve, 1997; García-Rodríguez et al., 2009; Koff et al., 1999).

There are conflicting findings regarding preserving FER ability for dynamic stimuli in the early stage of AD. Some studies, such as Goodkind et al. (2015), suggest that it is preserved, while others, like Martinez et al. (2018), indicate impairment. A study found that patients with dementia are less able to recognize positive emotions like joy and surprise but more able to recognize negative emotions like sadness and anger when they are displayed dynamically (Gkinopoulos et al, 2014).

3.2. Parkinson's Disease

Parkinson's disease (PD) is characterized by the pathological accumulation of α -synuclein aggregates in neurons, fibers, nerves or glial cells, causing lesions called LRP (Lewy-Related α -synuclein Pathologies) (McCann et al., 2014). This degeneration impacts the dopaminergic neurons of the substantia nigra, striatum, thalamus and subthalamic nucleus (Wolters, 2009). PD is associated with motor deficits, such as bradykinesia and tremors or, rigidity, tardively with postural instability, but also with non motor deficits, affecting cognitive abilities from mild to late stages (Svenningsson et al., 2012; Weintraub & Burn, 2011) as well as mood and personality (Tan, 2012).

Studies on the FER ability in PD are contradictory. Some studies showed no FER impairment (Ille et al., 2016; Pell & Leonard, 2005), while others showed impairment in this ability (Fortier et al., 2016, 2018). In addition, they were more deficient in recognition of negative emotions (anger, disgust, fear, and sadness) than positive emotions (joy, surprise) (Sedda et al., 2017), while other studies suggest that the recognition of negative emotions may be impaired firstly in the early stages of PD (Argaud et al., 2018; Assogna et al., 2010; Baggio et al., 2012; Coundouris et al., 2019; Gray & Tickle-Degnen, 2010; Kalampokini et al., 2016;

Sedda et al., 2017; Shafiei et al., 2020), then affecting recognition of positive emotions as the disease progresses (Lin et al., 2016).

REF ability in dynamic mode presentation is also impaired in PD (Argaud et al., 2016; McIntosh et al., 2015; Paulmann & Pell, 2010). On the other hand, some studies showed that FER performances did not differ between healthy elderly people and PD patients (Bek et al., 2020), and other studies showed a better performance in dynamic FER than static FER (Kan et al., 2002; Shafiei et al., 2020).

3.3. Fronto-Temporal Degeneration

Frontotemporal degeneration (FTD) is a progressive disease characterized by various symptoms, including personality and behavioral disorders, language deficits and impaired executive functions (The Lund & Groups Manchester, 1994). FTD includes three different phenotypes classically characterized according to the predominant clinical presentation and temporal atrophy patterns: the behavioral variant (bvFTD), the nonfluent variant and the semantic variant of primary progressive aphasia (Gorno-Tempini et al., 2011; Rascovsky et al., 2011).

In these three phenotypes, FER is impaired, especially for negative emotions (Oliver et al., 2015). FER impairments in patients with FTD have been linked to a decreased gray matter volume of the amygdala, insula, ventromedial prefrontal, and orbitofrontal cortices, with predominant involvement of the right side, as well as diffusion anomalies of the inferior longitudinal fasciculus and the inferior fronto-occipital fasciculus and the fornix (Bertoux et al., 2012; Downey et al., 2015).

Studies showed that dynamic FER ability is also impaired in FTD (Bertoux et al., 2020; Johnen & Bertoux, 2019). Especially, FER ability for negative emotions is more impaired than either on static (Fernandez-Duque & Black, 2005; Keane et al., 2002; Lavenu et al., 1999) or dynamic material (Goodkind et al., 2015; Werner et al., 2007).

3.4. Huntington's disease

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease (Huntington Study Group, 1996) with an extended CAG trinucleotide on chromosome 4 (Gusella et al., 1993). Neurocognitive disorders include not only memory and executive impairments (Craufurd & Snowden, 2002; Montoya et al., 2006) but also social cognition disorders such as FER impairment (Henley et al., 2012).

Studies also suggest that impairments in emotion recognition are evident for various stimuli other than faces, such as vocal or body language (Calder et al., 2010; de Gelder et al., 2008). Early studies on FER reported that there is a significant deficit in the recognition of disgust, which may be related to dysfunction of the basal ganglia and insula (Phillips et al., 1997; 1998; Sprengelmeyer et al., 1996; Thieben et al., 2002; Wicker et al., 2003). A meta-analysis showed that FER impairment concerns negative facial expressions that are linked to structural and functional dysfunctions of the striato-thalamo-cortical circuit, ventromedial prefrontal cortex, amygdala, and insula (Bora et al., 2016b). Impairment in recognizing negative facial expressions worsens as the disease progresses (Johnson et al., 2007; Tabrizi et al., 2009).

Research on dynamic FER ability in HD is limited, but findings show anger recognition is more accurate with vocal cues than dynamic material, and fear recognition is more impaired with dynamic material (Rees et al., 2014).

4. Consequences of facial emotion recognition impairment

FER ability allows individuals to understand others' intentions and messages to express and respond with accurate behavior. That's why poor FER ability could result in interpersonal difficulties (Carton et al., 1999; Feldman et al., 1991; Shimokawa et al., 2001). Below, the consequences of FER impairment will be defined.

4.1. Facial emotion recognition impairment and Behavioral and Psychological Symptoms of Dementia

Behavioral and psychological symptoms of dementia (BPSD) were defined by Finkel, (2001), as “*a heterogeneous range of psychological reactions, psychiatric symptoms, and behaviors resulting from the presence of dementia*”. Wide BPSD are characterized by a plentiful range of non-cognitive symptoms involving perception as hallucinations, mood as depression and anxiety, behavior as aggression and disinhibition, personality, and basic functioning (Ballard & Corbett, 2010; Craig et al., 2005; Finkel et al., 1997; Kosel et al., 2020; Zhao et al., 2016). In AD, BPSD are more common and a serious problem (Altomari et al., 2022), especially depression, anxiety and apathy that are found to occur before the onset of cognitive decline (Altomari et al., 2022; Johansson et al., 2020; Masters et al., 2015). They could predict both cognitive decline and progression from prodromal AD to dementia (Ma, 2020). Depression, anxiety, and apathy are the first and most frequent BPSD in the early onset of AD, other BPSD, such as agitation and irritability, appear as the disease progress (Laganà et al., 2022).

Damage in FER ability has been shown to correlate with BPSD (Gregory et al., 2002; Ibañez & Manes, 2012; Kempnich et al., 2018; Polet et al., 2022; Santamaría-García et al., 2016; Torralva et al., 2009). The findings showed a positive correlation between apathy, irritability, euphoria, disinhibition, aberrant motor behavior and poor FER ability in people with neurodegenerative disease (Kempnich et al., 2018; Polet et al., 2022; Santamaría-García et al., 2016).

4.2. Facial emotion recognition impairment and caregiver burden

As we have seen above, there is a correlation between FER impairment and BPSD. The ability to recognize and express emotions can impact communication between patient and caregiver, ultimately affecting their social interactions (Kordsachia et al., 2017). BPSD are also major factor in caregiver burden (Andrieu et al., 2003; Boutoleau-Bretonnière & Vercelletto,

2009; Finkel et al., 1997; Martinez et al., 2018). They have a major role in adverse caregiver outcomes, more than cognitive or functional symptoms (Ornstein & Gaugler, 2012; Schulz et al., 1995).

For caregivers whose care recipients are poor in FER ability and generate inappropriate emotional responses, there can be significant social disconnection, which may result in social isolation and caregiver burden (Brown et al., 2018; Cheng, 2017; Elferink et al., 2015; McCade et al., 2013; Miller et al., 2013; Narme et al., 2017; Phillips et al., 2010; Polet et al., 2021, 2022). Burden and stress would also impact the caregiver's social cognition abilities leading to a decrease in their theory of mind (Formica et al., 2020) and FER abilities (Martinez et al., 2018). The challenges faced by the caregiver could affect their understanding of their loved one's emotional and mental states, resulting in an added burden and potential increase in depression (Formica et al., 2020; Martinez et al., 2018).

4.3. Institutionalization

We previously saw that FER impairment leads to an increase in BPSD and, consequently, an increased caregiver burden. The latter is a factor in institutionalization (Chan et al., 2003). BPSD are not only associated with a high level of distress in the caregiver-patient couple, but also, with long-term hospitalization, misuse of medications and increased use of health-care services (Altomari et al., 2022; Brodaty et al., 2014; Eikelboom et al., 2019; Hongisto et al., 2018; Isik et al., 2019). Moreover, institutionalization determines a significant increase in the overall cost of dementia care, as well as and other costs are associated with BPSD (Herrmann et al., 2006; Schnaider Beerli et al., 2002).

BPSD are major reason for earlier institutionalization (Chan et al., 2003). In AD, delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, anxiety, and depression (Delfino et al., 2021) are correlated with caregiver burden and risk of

institutionalization (Boutoleau-Bretonnière & Vercelletto, 2009; Terum et al., 2017; Zhao et al., 2016).

Admitting a patient to an institution harms the psychological well-being of the patient (Cepoiu-Martin et al., 2016; Garity, 2006; Hermabessière, 2013; Sury et al., 2013) and their families and incurs high financial costs for them, and for society (Dufournet et al., 2019; Garity, 2006; Santamaría-García et al., 2016; Ylieff et al., 2011). Home care is 1.8 times less expensive (Wübker et al., 2015).



CHAPTER 2: EYE GAZE STRATEGIES DURING THE VISUAL EXPLORATION OF EMOTIONAL FACES

1. Eye-tracking: a method for recording eye gaze strategies.

The first eye-tracking devices date from the end of the 19th century and are used to study reading mechanisms (Javal, 1906). Nowadays, this device films the eye-movements with infrared cameras (Fig.1). It is a method to assess oculomotor functions (Leigh & Zee, 2015) to detect fixation distribution on observed stimulus, and its use as a research tool has significantly increased in recent years (Holmqvist et al., 2011). Eye movements and positions reveal crucial information about cognitive processes in human behavior by offering insights into visual information uptake and underlying mechanisms (Ashby et al., 2016). More precisely, tracking eye movements during facial expression interpretation reveals which parts of the face received the most attention (Manor & Gordon, 2003), which emotional information was extracted and allows to compare the scan path obtained from a group given to another group (Irwin, 2004; Smith et al., 2004; Schurgin et al., 2014; Calvo et al., 2018). Several variables and measures are traditionally considered in the study of eye-gaze strategies. (1) **Region of interest (ROI)**: during visual exploration, the visual scene (e.g., face) can be considered whole or be divided into ROI according to the salience or the relevance that area represents (e.g., eyes, nose, and mouth for facial observation). (2) **Number and duration of fixations**: the number of fixations is the indicator of visual exploration ability, and the duration of fixation is the indicator of disengagement/re-engagement from one target to another. Generally, a fixation is counted as soon as the eye remains immobile in a zone of 1° sideways for at least less than 100 ms (Manor & Gordon, 2003); (3) **Exploration duration**, also called “dwell time”, is the total time spent by looking at an ROI by adding the saccades¹ and fixations durations on that ROI.

¹ A rapid (as far as 800°/s) and abrupt (~ 150ms) movement of the eyes to move the fovea to an object of interest or to new information in the peripheral field (Lidersedge et al., 2011; Leigh & Zee, 2015).

Exploration duration accounts for the importance of an ROI within the visual scene. (4)

Scanpath: corresponds to the sequence of fixations and saccades on the visual scene (Noton & Stark, 1971), which allows searching particular information in a complex visual environment.

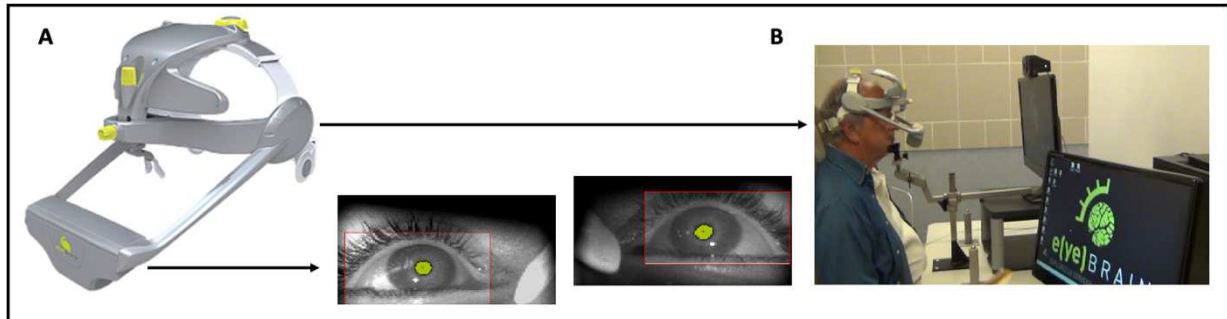


Fig. 1. Head-mounted eye-tracking device. **A.** Mobile EyeBrainT2® **B.** a participant during the eye-tracking paradigm.

2. Visual exploration of faces

Face perception is humans' most developed visual skill (Haxby et al., 2000). While scanning a visual scene, the face generates the greatest attention capture, even in the presence of other strongly salient elements (Flechsengar et al., 2018), this preference being present from early childhood (Kwon et al., 2016). While looking at a face, we simultaneously collect perceptual information about identity, sex, race, age, attractiveness, and personality (Fink et al., 2006; Todorov et al., 2008; Zebrowitz & Montepare, 2008; Zhao & Bentin, 2008). These pieces of information are mainly collected by scanning the most salient regions of the face located within an inverted triangle containing the eyes, nose and mouth (Janik et al., 1978; Yarbus, 1967).

The differences in eye-gaze strategies while exploring a face, particularly of the eye region, would account for the different interindividual recognition performances (Royer et al., 2018). Even if individuals rely on visual scanning routines to observe faces, there would be no universal and ideal scanpaths, these being idiosyncratic and dependent on the type of task and the individual's expertise (Kanan et al., 2015).

In the process of visually perceiving a scene, the vast amount of available information is filtered and only a small portion is attended to and processed, and this filtering is influenced by various factors that guide our attention (Rensink et al., 1997). This exploration is based on two attentional processes: (1) **Bottom-up attention orientation**, an early, effortless, automatic orientation of attention based on the visual characteristics of the stimuli (Cooper & Langton, 2006; Theeuwes, 1992; 2010). This type of visual exploration relies on the ventral fronto-parietal attentional network, composed of the right ventral frontal cortex and the right temporo-parietal junction (Corbetta & Shulman, 2002); (2) **Top-down attention orientation**, a slower, effortful, and controlled attention process based on the cognitive characteristics of the observer and depending on the observer's aims (Cooper & Langton, 2006; Itti & Koch, 2001; Yarbus, 1967). This type of visual exploration relies on the dorsal fronto-parietal attentional involving the prefrontal cortex and intraparietal sulcus (Mesulam, 1985; Corbetta & Shulman, 2002) together with the frontal eye fields (for generation of voluntary eye movements) (Barton, 2001; Petit et al, 1997). During attention-demanding tasks, the dorsal fronto-parietal attentional network is activated, while the default mode network is deactivated. The opposite occurs when the brain rests (Fox et al, 2005). This default network includes posterior cingulate cortex, medial prefrontal cortex, inferior parietal cortex and temporal cortex and is involved in introspection and emotional processing (as seen in part 2 "Facial emotion recognition ability in normal ageing").

It shows a greater activity while the individual is at resting state than at execution of a cognitive task (Chiong et al, 2013, Baez et al, 2016a; 2016b; Bastin et al, 2018, Multani et al, 2019). Another significantly involved network is the salience network in visual exploration, constituted by anterior cingulate cortex, ventromedial prefrontal cortex, insula, striatum and amygdala (Ciong et al, 2013; Baez et al, 2016a; 2016b; Day et al, 2013). The function of this salience network is crucial in detecting and focusing attention towards the most pertinent

stimuli in the surroundings, thereby facilitating and adjusting behavior accordingly (Barrett & Satpute, 2013; Day et al, 2013; Menon et al, 2015; Mutani et al, 2019).

Due to its specific physical characteristics, the presence of a face in the visual field of an individual leads to an important attentional capture generated by a bottom-up influence of attention orientation (Borji et al., 2013). The visual exploration of a face differs depending on whether the observer is trying to estimate age or to discriminate sex or facial expression (Peterson & Eckstein, 2012). This voluntary visual exploration of a face will be different according to the objective of the observer, under the aegis of the executive functions, which will generate a top-down mechanism of attention orientation to favour the search for specific visual information such as facial action unit during FER (Circelli et al., 2013; Torres et al., 2019). In this context, FER ability is a very fast process, and the first two fixations on the face are the most predictive for FER performance, these first two fixations being the most critical for face processing (De Sonneville et al., 2002; Schurgin et al., 2014). Below, we will define how we explore static and dynamic facial expressions.

2.1. Exploration of static facial expression

Healthy individuals mainly use visual information collected from the eye region for FER processing and distinguishing several emotional categories (Smith et al., 2005; Peterson & Eckstein, 2012). This region is critical for accurate FER ability, except for joy and disgust recognition, where observation of the mouth region is required (Ponari et al., 2012; Guarnera et al., 2017; Calvo et al., 2008; Adolphs et al., 2005; Eisenbarth et al., 2011). Below are the visual exploration patterns of static primary facial expressions highlighted by eye-tracking studies and illustrated in Figure 2.

Joy: while the eyes and mouth regions have the same proportions of the number of fixations (Eisenbarth & Alpers, 2011), the mouth region is a crucial region to recognize this facial expression (Calvo et al., 2008; Chaby, 2012; Schurgin et al., 2014). The mouth region being

observed earlier (Eisenbarth & Alpers, 2011, Calvo et al., 2018) and with longer fixation times (Eisenbarth & Alpers, 2011) compared to other ROIs.

Fear: as joy recognition, the eyes and the mouth regions have the same number of fixations (Eisenbarth & Alpers, 2011; Calvo et al., 2018). However, the eyes region seems crucial to recognize this facial expression (Adolphs et al., 2005; Calder & Young, 2005; Chaby, 2012; Schurgin et al., 2014).

Disgust: the mouth region is the most related ROI for this facial expression (Chaby, 2012; Schurgin et al., 2014). The nose region also seems important since it is observed earlier and longer than other ROIs (Calvo et al., 2018).

Sadness: recognition of the facial expression is strongly related to the eyes region (Calvo et al., 2018; Eisenbarth & Alpers, 2011; Schurgin et al., 2014), the first ROI observed, with more fixation, longer average fixation duration and longer dwell time spent on (Eisenbarth & Alpers, 2011; Calvo et al., 2018). The mouth region seems to be a secondary ROI in recognizing this facial expression (Calvo et al., 2008).

Anger: like recognition of sadness, recognition of this emotion is mainly related to the observation of the eyes region (Chaby, 2012; Schurgin et al., 2014), and this ROI is the first explored with a longer average fixation duration and more fixations (Eisenbarth & Alpers, 2011; Calvo et al., 2018).

Surprise: attention is captured equally on the eyes and mouth region (Calvo et al., 2018).

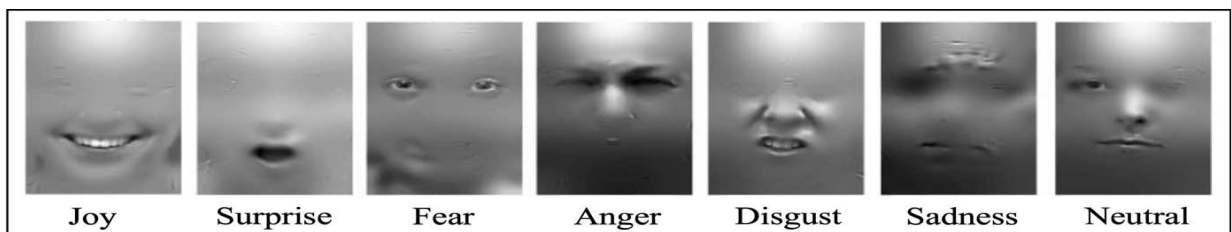


Fig. 2. Salience maps of each facial expression established with the bubble technic (Smith et al., 2005)

Facial expressions, when combined with gaze cues (gaze direction for example), can inform an observer about how an individual reacts emotionally to an environmental event (Chen

et al., 2021). For example, looking to the right while expressing fear indicates to his peers that potential danger is coming from the right (Chen et al., 2021). The ability to process and understand these gaze cues is considered an important adaptive mechanism for survival (Mathews et al., 2003; Tipples, 2006). Thus, several studies have shown that, when observing a face, the orientation of attention in the direction of others' gaze was faster when the face expressed an emotion than a neutral one (Chen et al., 2021). Anger is a special facial expression since its recognition is facilitated with a direct gaze, this type of angry face is considered more threatening than an angry face looking away (Graham & Labar, 2012). Anger is, therefore, more easily recognized in the case of direct gaze (Sander et al., 2007), the latter constituting an adaptative visual cue that facilitates recognition to prepare quickly for fight or fly.

2.2. Exploration of dynamic facial expression

Studies show that moving facial expressions are perceived to be more intense than static ones and that recognizing emotions is aided by temporal motion (Biele & Grabowska, 2006; Uono et al., 2010). Compared to static FER, dynamic FER is simpler and associated with stronger and widespread activation of specific brain regions dedicated to face processing, including the occipito-temporal areas that are face-specific: the fusiform face area located in the ventral pathway that facilitates low-level processing of various aspects of faces such as form or identity, and in the dorsal pathway: the posterior superior temporal sulcus and the inferior frontal gyrus are involved in processing changeable features, including facial motion such as gaze, mouth, and head movements, and facial expressions (Arsalidou et al., 2011; Haxby et al., 2000; O'Toole et al., 2002; Pitcher et al., 2011, 2014). The movement of the face triggers earlier activation in the brain which is thought to be due to an attentional mechanism that aids in the initial stages of visual encoding (Recio et al., 2011, 2014). This early activation in the visual processing regions of the brain persists for a longer duration in response to dynamic

expressions, indicating an increased demand for attention in decoding the complex features of moving faces (Perdikis et al., 2017; Recio et al., 2011, 2014; Wang & Yuan, 2021).

Studies found that while FER processing, the mouth region is the most salient region to discriminate across all facial expressions for dynamic presentations (Blais et al., 2012, 2017; Calvo et al., 2018; Hoffmann et al., 2013). However, others showed a greater amount of time devoted to fixating on the central region of the face during dynamic stimuli compared to static stimuli (Blais et al., 2017; Krumhuber et al., 2023; Roy et al., 2010). Focusing on the centre of a face helps extract motion information from across the entire face, aiding expression recognition (Blais et al., 2017; Plouffe-Demers et al., 2019). Eye-tracking studies have shown different gaze strategy in each facial expression, as follow:

Anger and sadness: the eye region is the most important for the recognition of these emotions with earlier and longer dwell time on the face region (Calvo et al., 2018; Lischke et al., 2012).

Joy: the mouth is the most important region to recognize this facial expression (Calvo et al., 2018; Lischke et al., 2012).

Disgust: the nose (and cheek) observation is most important to recognition with earlier and longer dwell time in this region (Calvo et al., 2018).

Fear: for some authors, observation of eye region is critical (Lischke et al., 2012), and for others, observation of the eye and mouth are equally important as observed for **surprise** recognition (Calvo et al., 2018).

Some authors studied the comparison of eye gaze strategies during FER in both static and dynamic conditions (Blais et al., 2017) (See Fig. 3). They found that observation of the eyes region for anger and the mouth region for disgust, joy, sadness, and surprise was similar whether the facial expression was static or dynamic. Nevertheless, the eyes region was more useful for the recognition of anger and surprise in the dynamic condition compared to the static

one. And the mouth region was more useful in the dynamic condition for the recognition of anger and sadness and was more useful in the static condition for the recognition of surprise.

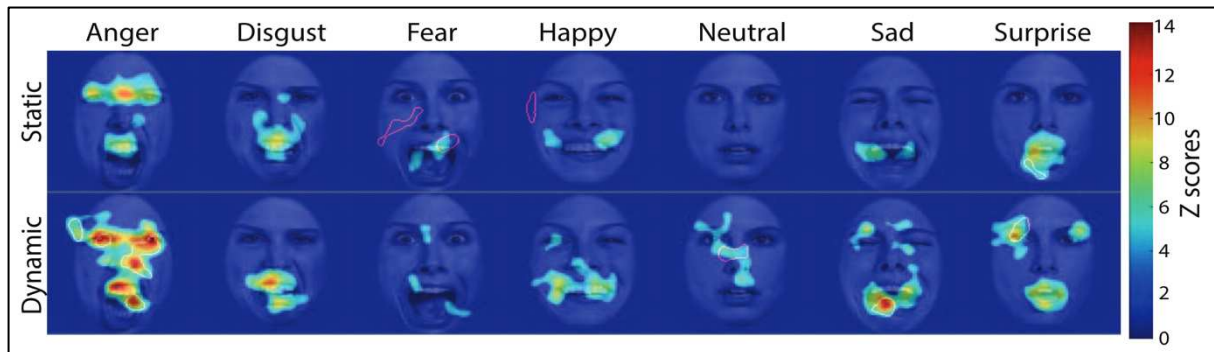


Fig. 3. Maps of visual information significantly correlated with accuracy in recognizing each expression in its static and dynamic versions. The areas outlined in white correspond to the information that was significantly more useful in one condition than in the other because of quantitative differences, and those outlined in red correspond to the information that was significantly more useful in one condition than in the other because of qualitative differences between the strategies (Blais et al., 2017).

3. Visual exploration of emotional faces in normal ageing

In the previous sections, we have seen that FER ability declines with ageing (Leime et al., 2013). Especially, elderly people are worse at recognizing negative facial expressions (Calder et al., 2003; Phillips et al., 2002; Suzuki et al., 2007; Wong et al., 2005). Age-related differences in emotion recognition may be affected by changes in visual attention processes and executive functions, as visual attention plays a significant role in FER (Wong et al., 2005; Circelli et al., 2013). Furthermore, evidence indicates variations in neural structures related to visual attention such as increased activation of the frontoparietal attentional network as compensation recruitment (Cabeza, 2004; Grady, 2001; Madden et al., 2007).

Age-related impairments in FER ability are more pronounced when faces are presented in static condition, compared to dynamic condition. That can be attributed to the fact that older adults have greater expertise in recognizing moving expressions, which have a higher emotional salience (Holland et al., 2019; Isaacowitz et al., 2007; Krendl & Ambady, 2010; Ziaei et al., 2021).

In the static FER process, elderly people have longer dwell time on the bottom half of the face (e.g., the nose-mouth region) than the top part of the face (e.g., the eyes region) which is the opposite of younger people (Birmingham et al., 2018; Chaby et al., 2017; Grainger & Henry, 2020; Murphy & Isaacowitz, 2010; Sullivan et al., 2007; Wong et al., 2005). Thus, the poor FER ability for negative emotions is explained by a smaller proportion of fixations on the top of the face, and the superior FER ability for disgust recognition is correlated with a greater proportion of fixations on the bottom half of the face (Wong et al., 2005). For joy and disgust recognition, young adults and elderly people, therefore, have a common visual exploration (Chaby et al., 2017). These two facial expressions are more related to the observation of the mouth region (Calvo et al., 2008; Chaby, 2012; Schurgin et al., 2014). This exploration strategy would explain that FER of joy and disgust, and to a lesser extent, surprise facial expressions are preserved in ageing (Chaby et al., 2017; Circelli et al., 2013; Ruffman et al., 2008; Wong et al., 2005), or even would improve with ageing (Calder et al., 2003; Circelli et al., 2013; Ruffman et al., 2008; Suzuki et al., 2007; Wong et al., 2005).

For example, a study comparing FER ability in three different ROI conditions (whole face, eyes only and mouth only), has shown that elderly people were worse at recognizing anger and sadness facial expressions from eyes but better to recognize them from the mouth compared to younger adults (Slessor et al., 2022). When facial expressions were constructed by combining incongruent emotional facial regions (e.g., angry eyes with a sad mouth), elderly people were again more likely to use information from the mouth to recognize anger, fear, and disgust (Slessor et al., 2022). Observation of the mouth region during FER is favored by elderly individuals. According to some authors, this observation bias of the mouth would be linked to hearing loss, leading to mouth focusing for lip reading during a conversation (Chaby et al., 2017). Hearing loss would be another explanation for this bias in addition to the modification of eye-strategies.

4. Visual exploration of emotional faces in Alzheimer's disease and related syndromes

In many studies, it has been highlighted that FER ability impairment is associated with modifications in eye-gaze strategies during the observation of emotional faces. Usually with a decreased observation of the eyes, whether in psychiatric disease as schizophrenia or social phobia (Williams et al., 2003, Horley et al., 2004), or neurological diseases such as multiple sclerosis (Polet et al, 2023), or focal epilepsy (Metternich et al., 2022).

Such modification in visual exploration of emotional faces also concerns NDD such as AD, bvFTD and PD (Clark et al., 2010; Hutchings et al., 2018; Ogrocki et al., 2000; Polet et al., 2017, 2022). Studies showed fewer fixations on the eye region in bvFTD (Hutchings et al., 2018), or a shorter dwell time in the scanning of emotional faces and fewer fixations on the eye region in AD (Ogrocki et al., 2000), which indicates a loss of salience in different ROI of the face as reported in autism (Hernandez et al., 2008). However, in AD, the fear can be recognized if the attention is directed to the eyes (Hot et al., 2013), and FER performances improved when the emotional salience of the faces was increased (at a high intensity of facial expressions) in AD (Phillips et al., 2010) and bvFTD (Kumfor et al., 2011), suggesting attentional origin to FER impairment. In individuals with PD, a subtle impairment in their visual exploration of facial expressions has been reported (Clark et al., 2010). This result is in line with Polet et al., (2017; 2022) studies wherein FER impairment has been linked to a slight modification of the eye gaze strategy in AD and PD, compared to bvFTD for whom this modification was important (with complete loss of emotional salience of facial regions, expressive faces being observed as neutral faces). Furthermore, these latter studies showed a link between FER impairment, modification of eye-gaze strategies during exploration of emotional faces and BPSD in these samples.

To our knowledge, there is only one study which investigated visual exploration during dynamic FER in a neurodegenerative disease study, conducted in PD compared to healthy elderly people (Bek et al., 2020). This study showed that (1) while healthy elderly people had a benefit from dynamic facial expressions, patients with PD did not show an advantage; (2) in dynamic FER, patients with PD had greater dwell time on the mouth region compared to controls, and control group also showed shorter dwell time on the eye region while FER. These subtle differences between groups would also align with the other studies on static FER ability (Clark et al., 2010; Polet et al., 2017; 2022). The slight variations in eye gaze strategies in PD could be attributed to the stage of the disease (Bek et al., 2020). Their sample may not have been at an advanced enough stage to display any impairments in visual exploration, as such impairments may only become noticeable in later stages or in individuals with more severe cognitive impairment (Archibald et al., 2013; Kennard et al., 1994).



CHAPTER 3: COGNITIVE REMEDIATION OF FACIAL EMOTION RECOGNITION ABILITY

1. Experimental paradigms improving facial emotion recognition

Patient SM showed that it was again possible to recognize the facial expression of fear when attention was forced on the eyes, despite bilateral amygdala damage (Adolphs et al., 2005). Accordingly, paradigms for altering/influencing gaze strategies when scanning emotional faces could lead to improved recognition of facial expressions. For example, improvement for fear recognition were also found in AD patients (Hot et al., 2013), the training giving keys/strategy to compensate for amygdala impairment. These paradigms consist of the imposition of top-down search strategies for looking for emotional cues on faces. In this previous instance, there is an important role in the attention orientation to the eyes, which is well-known in fear recognition (Adolphs et al., 2005; Eisenbarth & Alpers, 2011; Schurgin et al., 2014). As attention orientation improves recognition, FER impairment would no longer be linked to an alteration of emotion processing but rather to an atypical eye-gaze strategy while scanning the facial emotional cues, which refers to a disturbance in the attention orientation (Adolphs et al., 2005; Spezio et al., 2007).

Bottom-up attention orientation paradigms can also improve FER ability performances. For example, FER performances can be improved if emotional cues are more salient by increasing their intensity in AD and bvFTD (Phillips et al., 2010; Kumfor et al., 2011). Some studies indicate that individuals with mild AD have more challenges identifying emotions that are relatively less intense, such as those at a 60% level (Bediou et al., 2009) or at a 75% level (Phillips et al., 2010), and other studies also show that recognition difficulties are most pronounced for subtler emotions (at low intensity) (Bediou et al., 2009; Jiskoot et al., 2021; Kohler et al., 2005; Phillips et al., 2002; Sapey-Triomphe et al., 2015; Spoletini et al., 2008; Weiss et al., 2008).

2. Different rehabilitation programs targeting facial emotion recognition ability

A systematic review of social cognition training and remediation interventions found that improving emotional processing, including FER, is a common goal (Fernández-Sotos et al., 2019). To date, most cognitive interventions for enhancing FER have been designed for patients with schizophrenia, wherein this impairment is well-established (Addington et al., 2006; Gao et al., 2021; Streit et al., 1997). Below we will define some of the FER targeted programs most used in routine care.

-Gaïa Training Program (Gaudelus and Franck, 2012) is an individualized training program that consists of 20 sessions and uses a support video. The Gaïa program has three phases: (1) an exercise with photographs to develop strategies for recognition and distinguishing joy, anger and sadness expressions; (2) a computerized exercise consisting of videos, aiming to adapt the strategies developed at the first phase to dynamic situations (with five levels of increasing difficulty); (3) a generalization phase concerning at least five therapist-participant sessions and computerized exercises finalized according to the participant's profile and demands, to recognize and distinguish other facial expressions (fear, disgust and contempt) and to work on complex emotions. This program has led to a significant improvement in performance with schizophrenic patients (Gaudelus et al., 2016).

-Micro Expressions Training Tool (METT) (Ekman, 2002) is a self-guided online training program that is developed to help individuals learn to recognize subtle facial expressions. The program is based on an attentional hypothesis which postulates that primary difficulties in the field of attention would disturb the visual exploration of faces in schizophrenia and would result in an impairment in the detection of emotions. For this reason, the program explicitly directs the individual's attention to the key features of facial regions (action units) that detect emotions (Peyroux et al., 2013). The program consists of didactic videos that present pairs of emotions that are often confused (anger/disgust; contempt/joy; fear/surprise; fear/sadness), emphasizing

the elements that allow these emotions to be differentiated. At the end of each video, an image depicting the entire facial expression worked on is presented. This comprises 28 images presenting micro-expressions (a micro-expression is an emotion presented <500 ms between two neutral expressions). The objective for the patient is to detect the emotion that has been presented, if this fails, feedback of representing the image is provided. An improvement in FER ability was found in schizophrenia following the METT program (Russell et al, 2006, 2008).

-Training of Affect Recognition (TAR) (Fromman et al., 2003) was initially developed for patients with schizophrenia, and has been shown to have beneficial effects on their FER ability (Frommann et al., 2008). It comprises three modules, each consisting of four sessions, for a total of 12 sessions. The TAR program includes various exercises (computerized, paper-pencil exercises, and exercises the patient should do at home) based on the following principles: (1) errorless learning (Wilson et al., 1994) with the avoidance of errors during training; (2) over-learning, with a high-frequency repetition of prototypical facial expression features (e.g., lower lip pushed upwards, upper lip raised and wrinkled nose for disgust recognition); (3) the abstraction of facial features, abstraction of individual features to prototypical expressions, combined with alternative cognitive strategies such as verbalization, self-instruction and generation of associations using cues/anchors. In the first module, participants learn to distinguish between primary facial expressions in a didactic way on the principles of the Facial Action Coding System (Ekman & Friesen, 1976). Participants' attention is drawn to the particularities of the face associated with each facial expression. Exercises are based on the blurring of aids (Vallat-Azouvi & Le Bornec, 2013) and spaced retrieval (Camp et al., 1996), allowing a gradual increase in difficulty and the automation of the strategies of visual search. The second module aims to promote a more holistic treatment of the emotional face, to increase the speed of the FER, to be able to discriminate between ambiguous emotions and to encourage the participant to rely on their first impression. The difficulty increases by gradually decreasing

the intensity of the emotions and the presentation time stimuli and degrading certain parts of the face. Finally, the third module aims to integrate these learnings for recognizing emotions in social situations of daily life and ambiguous emotions. The participants are invited to compare their impressions with the context elements to assign emotional and mental states (the program gradually evolves to affective theory of mind exercises).

3. Effects of a cognitive rehabilitation program for the recognition of facial emotion in Alzheimer's Disease

García-Casal et al. (2017) provided the first example of using cognitive rehabilitation to improve FER ability in individuals with AD, using the TAR program. Their study compared FER performances in three AD groups: (1) a group receiving the TAR program (n=11); (2) another group receiving cognitive stimulation sessions (n=11) and (3) a group without any cognitive intervention (n=11). Only the group that received rehabilitation for FER showed significant improvement in their performance, especially in recognizing surprise, disgust, and neutral expressions, as well as in their recognition speed. These improvements were still present one month after treatment ended. This study demonstrates that it is possible to rehabilitate FER in individuals with NDD, even if they have cognitive, attentional and memory impairments.

Based on these significant results, a preliminary study, named EYE-TAR (MA) (Polet et al., 2021), was conducted to measure the effects of FER remediation in AD and the impacts on visual scanning, BPSD and caregiver burden. This study involved applying the TAR program to a sample of 4 AD patients and comparing it to another sample of 4 AD patients who underwent a classical cognitive stimulation program (CS). FER ability using pictures from Ekman's Face Test (Ekman and Friesen, 1976), a static FER ability assessment, before and after the interventions. Eye-gaze strategies during FER were recorded using an eye-tracking device (number and duration of fixations as well as dwell time in the eyes, nose and mouth region).

And the caregiver completed the NPI scale (Cummings et al. 1997) for BPSD assessment and the Zarit scale (Zarit et al., 1985) for the level of burden.

Like Garcia-Casal et al. (2017), results showed that the group that underwent the TAR program exhibited significant improvements in their FER ability (particularly for recognition of sadness, fear and neutral condition), and they also demonstrated modifications in their eye gaze strategies during the observation of emotional faces, specifically an increase in the observation of the eyes region. Furthermore, this group showed a decrease in BPSD and caregiver burden. These beneficial effects were sustained at the 1-month post-intervention follow-up.

These results suggest that even though AD is a neurodegenerative disease, it is still possible to successfully carry out a remediation program. The application of this program allowed individuals to be able to improve their ability to scan emotional faces, making them more proficient in FER processing (decreased response time). This indicates that in AD, impairment in FER is closely linked to difficulties with attention orientation on the face. One effective way to address both BPSD and the caregiver's burden would be the enhancement of FER ability.



PART II: PROBLEM STATEMENT

CHAPTER 4: PROBLEM STATEMENT

The literature review of **Chapters 1, 2 and 3** shows that

1. FER ability is one of the social cognition skills and plays a critical role in social interactions. FER ability relies on the functioning of many other cognitive abilities (like information processing speed, executive functions, attention, working memory, semantic knowledge, and visuo-perceptual ability) and on many brain structures (such as the somatosensory cortex, the superior temporal sulcus, the orbitofrontal cortex, the basal ganglia, the insula, the temporal lobes, the amygdala and the fusiform gyrus) interconnected within the “social brain networks” via numerous association fasciculus of white matter.

2. The involvement of cerebral areas distributed over the entire brain makes the FER an ability weakened with ageing and impaired in NDD such as AD.

3. Poor FER ability is negatively correlated with BPSD level in NDD (especially apathy, irritability, euphoria, disinhibition, and aberrant motor behavior). In addition, BPSD is the main factor in the level of family caregiver burden, which increases the risk of institutionalization when the latter is high. Therefore, the more FER ability is impaired, the higher the family caregiver’s burden is likely.

4. When FER is impaired, a modification in the visual scanning patterns of facial expressions is systematically observed. This indicates that the facial regions with high emotional salience (eyes, nose and mouth) intended to attract the gaze to decode the emotion expressed, no longer attract the gaze similarly. Visual scanning occurs through two attentional processes: an automatic, bottom-up process and a voluntary, top-down process, dependent on fronto-parietal attentional networks functioning in interaction with other networks, such as the default mode and saliency networks, also involved in social cognition skills. Therefore, the abilities involved in visual information retrieval are equally susceptible to normal and pathological ageing.

5. Experimental paradigms have shown that when attention was directed to the upper part of an expressive face, FER performance was enhanced, even in NDD. Thus, these results showed that it was possible to consider remediation of FER in NDD.

6. While this approach has demonstrated its effectiveness in diseases such as schizophrenia, to our knowledge, only two studies have attempted to apply a cognitive remediation program of FER to people with NDD. Both studies applied the TAR program to people with AD. The first (Garcia-Casal et al., 2017) showed a significant improvement in FER performance with the maintenance of this effect 1-month after the end of the program. The second (Polet et al., 2021), based on small sample sizes, confirmed these results, and also showed a modification of eye-gaze strategies (increased fixation duration and greater observation of the upper part of the face), a reduction in the level of BPSD and family caregiver burden following the TAR program.

The present literature review and especially the experimental results from the studies have applied the cognitive remediation program of FER ability, supporting the “triple interaction” hypothesis, stipulating that visual exploration strategies, FER ability and BPSD are linked (Polet et al., 2022).

Despite some promise in using cognitive remediation programs that focus on FER to manage BPSD in AD patients, the current results have been achieved using static facial expressions, which are unecological material. In addition, these two studies (Garcia-Casal et al., 2017; Polet et al., 2021) are based on the same cognitive program, which does not allow a comparison of the effectiveness of two different approaches to improve FER in NDD. Furthermore, the benefits observed on family caregiver burden and BPSD levels were obtained in small samples (Polet et al., 2021) and therefore need to be confirmed in a larger sample. Finally, the positive results of these two studies were maintained for one month, but little is

known about the longer-term effects of this kind of cognitive remediation approach on people with NDD.

Based on the problem statement, our first objective was to draw up an inventory of existing methods used to improve FER and to study their effectiveness within NDD to identify the most effective and appropriate method for this population. Then, our second objective was to confirm the results obtained with the TAR program in people with AD (namely, an improvement in the FER ability together with a modification of the visual exploration strategies of faces and a decrease in the levels of BPSD and family caregiver burden), by using a more ecological dynamic FER assessment and with a larger sample size. Finally, the last objective was to study the long-term effect (more than 2 years later) of the cognitive remediation program of FER on people with AD and their family caregivers.

Based on these objectives, we designed and set up the following three studies:

Study 1: a systematic review and meta-analysis presented in **Chapter 5**.

Study 2: EYE-TAR (AD+) presented in **Chapter 6**.

Study 3: EYE-TAR (MA) *Follow-up* presented in **Chapter 7**.

Below, they are briefly described.

1.Can the ability to recognize facial emotions in neurodegenerative diseases be improved?

To begin the thesis work, we first identified all the interventions used in research to improve FER ability in NDD. We gathered data to compare their effectiveness, explore the duration of their effects, and examine their possible impacts on BPSD and caregiver burden. This information is valuable in confirming the context and direction for our future studies on this topic.

Then we conducted a systematic review and meta-analysis according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Page et al., 2021).

The systematic review consisted of to find relevant studies published between January 2011 and December 2021 on “Alzheimer's disease”, “neurodegenerative disease”, “dementia”, “remediation”, “emotion”, and “facial expressions” by using the PsycInfo, PsycArticles, Embase, Scopus, and PubMed databases. Articles were eligible if they studied interventions to improve FER ability in individuals with any NDD. The type of article was limited to randomized-controlled, nonrandomized-controlled, and nonrandomized-noncontrolled studies. Articles were excluded if they studied diseases other than NDD, assessment of emotion recognition other than the FER test, and lack of intervention to improve FER ability. Also, articles in languages other than English or French, case studies, and review articles were excluded. Then, the meta-analysis was conducted from the articles that provided sufficient data to calculate effect sizes.

2. Facial emotion recognition ability remediation in people with Alzheimer's disease: what are the short-term benefits for the patient and the family caregiver? (EYE-TAR (AD+) study)

This second study, titled “EYE-TAR (AD+)”, had the main objective confirming the results of the preliminary study “Rehabilitation of facial emotion recognition in Alzheimer's disease and effects on observational strategy, behavioral disorders and family caregiver burden” (Polet et al., 2021) published in *Neurologie, Psychiatrie, Gériatrie* (see Appendix 1). This study showed that a FER targeted remediation program named TAR improved the FER ability and modified the eye gaze strategies during the observation of emotional faces (specifically an increase in the observation of the eyes region), with a decreased BPSD and caregiver burden, benefits maintenance 1-month post-intervention follow-up.

Following these results, we had the ambition to measure the effects of the TAR program on a larger sample size of people with AD and with a more ecological assessment of FER ability. To address this issue, we established the EYE-TAR (AD+) study.

Conducted in 24 AD patient-caregiver couples, EYE-TAR (AD+) is a randomized controlled single-blinded study. Participants are divided into either in AD-TAR group (n=12) allocated to the TAR program or in AD-CS group (n=12) allocated to a cognitive stimulation program. The number and frequency of program sessions were identical between the two groups (2 sessions/week for 6 weeks). Before, at the end and 1-month post-intervention, FER ability was assessed within static material (Ekman's faces set, Ekman & Friesen, 1976) and with dynamic material (ADFES, Van der Schalk et al., 2011) to have a more ecological condition. Eye-gaze strategies on key areas of the face (number and duration of fixations as well as time spent in the eyes, nose, and mouth region) were recorded by an eye tracker. The caregivers completed the NPI scale (Cummings et al., 1997) for BPSD and the Zarit scale (Zarit et al., 1985) for the level of the burden.

3. Facial emotion recognition ability remediation in people with Alzheimer's disease: what long-term benefits for the patient and the family caregiver? (EYE-TAR (MA) Follow-up study)

The preliminary study EYE-TAR(MA), titled “Rehabilitation of facial emotion recognition in Alzheimer’s disease and effects on observational strategy, behavioral disorders and family caregiver burden” (Polet et al., 2021), published in *Neurologie, Psychiatrie, Gériatrie* (see Appendix 1), showed that beneficial effects of the TAR program were sustained at the 1-month post-intervention follow-up. Regarding a progressive disease like AD, how can we ensure the long-term maintenance of these positive effects on both patients and caregivers?

The main objective of the present study, titled “EYE-TAR (MA) *Follow-up*”, was to assess the long-term (> 2 years) impact of the remediation of FER ability by the TAR program on FER performances, eye-gaze strategies, BPSD and family caregiver burden levels. It was an observational, prospective, descriptive, comparative designed study.

More than 2 years apart, we included patient-caregiver couples who had participated in the EYE-TAR (MA) study (participants who had received the TAR program (n=4) and a cognitive stimulation program (n=4)). These are patients still being followed as part of routine care at the Rainier III Memory Centre.

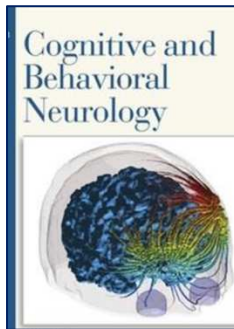
We assessed FER ability by Ekman’s Faces Set (Ekman & Friesen, 1976), with eye-gaze strategies on key regions of the faces (number and duration of fixations as well as time spent in the eyes, nose and mouth region) recorded by an eye-tracker device. And the caregivers completed the NPI scale (Cummings et al., 1997) for BPSD assessment and the Zarit scale (Zarit et al., 1985) for the level of the burden.





PART III: ARTICLES

CHAPTER 5: Article 1 (Systematic Review and Meta-analysis). Can the ability to recognize facial emotions in neurodegenerative diseases be improved? A systematic review and Meta-analysis



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REVIEW

OPEN

Can the Ability to Recognize Facial Emotions in Individuals With Neurodegenerative Disease be Improved? A Systematic Review and Meta-analysis

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ABSTRACT

Background: Facial emotion recognition (FER) is commonly impaired in individuals with neurodegenerative disease. This impairment has been linked to an increase in behavioral disorders and caregiver burden.

Objective: To identify interventions targeting the improvement of FER ability in individuals with neurodegenerative disease and investigate the magnitude of the efficacy of the interventions. We also wanted to explore the duration of the effects of the intervention and their possible impacts on behavioral and psychological symptoms of dementia and caregiver burden.

Method: We included 15 studies with 604 individuals who had been diagnosed with neurodegenerative disease. The identified interventions were categorized into three types of approach (cognitive, neurostimulation, and pharmacological) as well as a combined approach (neurostimulation with pharmacological).

Results: The three types of approaches pooled together had a significant large effect size for FER ability improvement (standard mean difference: 1.21, 95% CI = 0.11, 2.31, $z = 2.15$, $P = 0.03$). The improvement lasted post intervention, in tandem with a decrease in behavioral disorders and caregiver burden.

Conclusion: A combination of different approaches for FER ability improvement may be beneficial for individuals with neurodegenerative disease and their caregivers.

Key Words: facial emotion recognition, neurodegenerative disease, cognitive rehabilitation, neurostimulation, pharmacological intervention

Abbreviations: **AD** = Alzheimer disease. **BPSD** = behavioral and psychological symptoms of dementia. **bvFTD** = behavioral variant of frontotemporal dementia. **FER** = facial emotion recognition. **HD** = Huntington disease. **METT** = micro expressions training tool. **MMSE** = Mini-Mental State Examination. **NDD** = neurodegenerative disease. **PD** = Parkinson disease. **SMD** = standard mean difference. **SSRI** = selective serotonin reuptake inhibitor. **STN** = subthalamic nucleus. **STN-DBS** = subthalamic nucleus deep-brain stimulation. **TAR** = training on affect recognition. **tDCS** = transcranial direct current stimulation.

1.INTRODUCTION

Facial emotion recognition (FER) plays a crucial role in communication and interpersonal interactions (Hutchings et al, 2017). This social cognition ability provides valuable information to an individual, enabling him or her to respond appropriately to different social situations. Joy, fear, disgust, sadness, surprise, and anger are basic and universal emotions (Ekman and Friesen, 1976).

Poor FER ability has been shown to correlate with behavioral and psychological symptoms of dementia (BPSD) (Gregory et al, 2002; Ibáñez and Manes, 2012; Kempnich et al, 2018; Polet et al, 2022; Santamaría-García et al, 2016; Shimokawa et al, 2001; Torralva et al, 2009), thereby impairing social relationships (Brown et al, 2018; Miller et al, 2013; Narme et al, 2017; Polet et al, 2021, 2022). More specifically, apathy, euphoria, disinhibition, and aberrant motor behavior have been negatively correlated with FER ability (Kempnich et al, 2018; Polet et al, 2022). For caregivers whose care recipients are unable to recognize emotions and generate appropriate emotional responses, there can be significant social disconnection, which may result in social isolation and caregiver burden (Brown et al, 2018; Cheng, 2017; Miller et al, 2013; Narme et al, 2017; Polet et al, 2021, 2022).

Is FER Impaired in Neurodegenerative Disease?

FER ability deteriorates during normal aging (Virtanen et al, 2017; Williams et al, 2009) and is impaired in individuals with neurodegenerative disease (NDD) (Bora et al, 2016a; Fortier et al, 2018; Marcó-García et al, 2019). Changes at the neuroanatomical level of the FER ability network, including the amygdala, cingulate cortex, and orbitofrontal cortex, have been shown to be associated with changes in FER ability (De Winter et al, 2016; Porcelli et al, 2019).

FER in Alzheimer Disease

A recent meta-analysis concluded that the FER ability of individuals with Alzheimer disease (AD) is preserved for joy recognition and is most reduced for negative emotions such as fear, anger, disgust, and sadness (Fernández-Ríos et al, 2021). The principal cause of FER impairment in AD is dysfunction of the temporoparietal regions (Cadieux and Greve, 1997; Ossenkoppele et al, 2015; Teng et al, 2007). In particular, a study indicated that an impairment of FER for negative emotions could be the consequence of an alteration of the uncinate fasciculus, which connects the prefrontal cortex to the anterior temporal cortex (Takahashi et al, 2020). Another explanation for FER impairment could be a slight modification of the visual scanning strategy during FER (Polet et al, 2017, 2022).

FER in the Behavioral Variant of Frontotemporal Dementia

Social cognition impairment is primary, severe, global, and present in individuals with the behavioral variant of frontotemporal dementia (bvFTD) from the early stage of the disease (Christidi et al, 2018; Fortier et al, 2016, 2018; Gregory et al, 2002; Kemp et al, 2012). This severe impairment is related to an impairment in the perception of emotional and social cues (Baez et al, 2016; Cohen et al, 2016; Sturm et al, 2015; Werner et al, 2007). FER ability impairment in individuals with bvFTD is greater for negative emotions compared with positive emotions (Diehl-Schmid et al, 2007). The principal cause of FER ability impairment in bvFTD can be explained by atrophy of the orbitofrontal cortex, insula, and amygdala (Kumfor et al,

2013). Furthermore, FER ability impairment has been linked to an important modification of the visual scanning strategy (Polet et al, 2017, 2022).

FER in Parkinson Disease

Facial emotion identification, discrimination, and matching tasks have shown that FER ability is impaired in individuals with Parkinson disease (PD) (Argaud et al, 2018; Gray and Tickle-Degnen, 2010). Such impairment is greater for negative emotions in the early stages of the disease (Argaud et al, 2018; Assogna et al, 2010; Baggio et al, 2012; Coundouris et al, 2019; Gray and Tickle-Degnen, 2010; Kalampokini et al, 2016; Kemp et al, 2012; Sedda et al, 2017; Shafiei et al, 2020), whereas FER ability impairment for positive emotions such as joy and surprise occurs in later stages of the disease (Lin et al, 2016). The principal cause of FER ability impairment in PD is dysfunction of the amygdala, orbitofrontal cortex, superior frontal gyrus, and posterior cingulate gyrus (Baggio et al, 2012; Heller et al, 2018; Ibarretxe-Bilbao et al, 2009; Péron et al, 2012; Robert et al, 2014; Wabnegger et al, 2015), as well as an increase in somatosensory cortex activity (Wabnegger et al, 2015). As observed in AD, FER ability impairment is also linked to a slight modification of the visual scanning strategy (Polet et al, 2017, 2022).

FER in Huntington Disease

FER ability impairment is present in the presymptomatic stage of Huntington disease (HD) (Henley et al, 2008; Johnson et al, 2007; Stout et al, 2012), can be detected as early as 15 years before the onset of symptomatic HD, and worsens with disease progression (Labuschagne et al, 2013; Tabrizi et al, 2009). In a meta-analysis of social cognition in individuals with HD, FER ability impairment was associated with negative emotions related to structural and functional abnormalities in the striato-thalamo-cortical circuit, ventromedial prefrontal cortex, amygdala, and insula (Bora et al, 2016b).

Ways to Improve FER Ability

There are a variety of interventions that can be undertaken to improve FER ability.

Cognitive (Nonpharmacological) Approach

A systematic mapping review of cognitive rehabilitation interventions in social cognition showed that emotion processing is often targeted for improvement (Fernández-Sotos et al, 2019). Thus far, most of the cognitive approaches to improving FER ability have been developed for individuals with schizophrenia.

Training of Affect Recognition Program. The Training of Affect Recognition (TAR; Frommann et al, 2003) program consists of three modules, each consisting of four sessions, for a total of 12 sessions. The first module aims to identify and discriminate the prototypical facial signals of the six primary emotions. The second module promotes the holistic processing of emotional faces and faster recognition and distinction of low-intensity expressions. The third module addresses the recognition of emotions in social situations as well as ambiguous emotions. This program was developed for individuals with schizophrenia and has been shown to have beneficial effects on their FER ability (Frommann et al, 2008).

Gaïa Training Program. Gaïa (Gaudelus and Franck, 2012) is an individualized training program that consists of 20 sessions and uses a support video. Beneficial effects of Gaïa on symptoms and social functioning through improved FER ability have been found among individuals with schizophrenia (Gaudelus et al, 2016).

Micro Expressions Training Tool. The micro expressions training tool (METT; Ekman, 2002) is a self-guided online training program that is designed to help individuals learn to recognize subtle facial expressions. It explicitly directs the individual's attention to the key features of facial regions (action units) that detect emotions (Peyroux et al, 2013). Studies have shown an improvement in FER ability among individuals with schizophrenia following this training program (Russell et al, 2006, 2008).

Neurostimulation Approach

Noninvasive techniques, such as repetitive transcranial magnetic stimulation and transcranial direct current stimulation (tDCS), can modulate brain activity and connectivity (Shafi et al, 2012), thereby selectively improving or disrupting behavior (Bikson and Rahman, 2013). Faster FER ability was found during anodal or cathodal tDCS over the left dorsolateral prefrontal cortex, with a significant effect during anodal tDCS for positive emotions in a healthy population (Nitsche et al, 2012). In a healthy male population, faster FER ability of negative stimuli was found using anodal and cathodal tDCS over the right and left dorsolateral prefrontal cortex, respectively (Conson et al, 2015).

Deep brain stimulation (DBS), an invasive technique, is the most effective treatment for movement disorders. It targets the subthalamic nucleus in individuals with PD (Bronstein et al, 2011; Mahlknecht et al, 2015). The cortico-subcortical network, which includes the basal ganglia, has been implicated in the facilitation or inhibition of movements, as well as in the selection of behaviors, emotions, and thoughts (Kalampokini et al, 2020).

Pharmacological Approach

A systematic mapping review of pharmacological rehabilitation interventions in social cognition included a number of important studies on the use of hypothalamic hormones, particularly oxytocin, followed by neuroleptics (risperidone and olanzapine) and psychostimulants (amphetamines) (Fernández-Sotoz et al, 2018). For example, it has been shown that intranasal oxytocin stimulates key brain regions associated with FER ability, such as the amygdala and the prefrontal (Labuschagne et al, 2010, 2012) and striatum cortices (Feng et al, 2015; Nawijn et al, 2017). Selective serotonin reuptake inhibitors (SSRIs), along with serotonin augmentation in the form of serotonin precursor tryptophan, have been shown to significantly improve FER ability in healthy individuals (Attenburrow et al, 2003; Browning et

al, 2007; Harmer et al, 2003). Also, a study showed that dopaminergic therapy increased FER ability in individuals with PD (Dan et al, 2019).

Current Study

The first aim of our review was to identify several types of interventions targeting the improvement of FER ability in individuals with NDD and investigate the magnitude of their efficacy. The second aim was to explore the duration of their effects and their possible impacts on BPSD and caregiver burden.

2.METHODS

Study Selection

We conducted our systematic review and meta-analysis according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Page et al, 2021). Supplementary material 1 contains a copy of our completed checklist. The literature search was conducted using the PsycInfo, PsycArticles, Embase, Scopus, and PubMed databases to identify studies that had been published between January 2011 and December 2021 using the following combination of key words: “Alzheimer's disease,” “neurodegenerative disease,” “dementia,” “remediation,” “emotion,” and “facial expressions.” We reviewed the reference lists of the retrieved articles to identify additional records.

The selection procedure is illustrated in Figure 1. Three authors (N.M., K.P., and S.H.) independently screened the articles for eligibility. Articles were considered to be eligible if they studied interventions to improve FER ability in individuals with any NDD. The type of article was limited to randomized-controlled, nonrandomized-controlled, and nonrandomized-noncontrolled studies. The exclusion criteria were disease other than NDD, assessment of emotion recognition other than the FER test, and lack of intervention to improve FER ability. Articles in a language other than English or French, case studies, and review articles were excluded.

Data Extraction

We extracted the data in an Excel spreadsheet with the following headings: (a) author and year of publication, (b) type of disease, (c) sample size, (d) allocation of groups (experimental vs control), (e) type of intervention approach, (f) type of assessment, (g) outcomes measures, (h) availability of follow-up data, and (i) main findings.

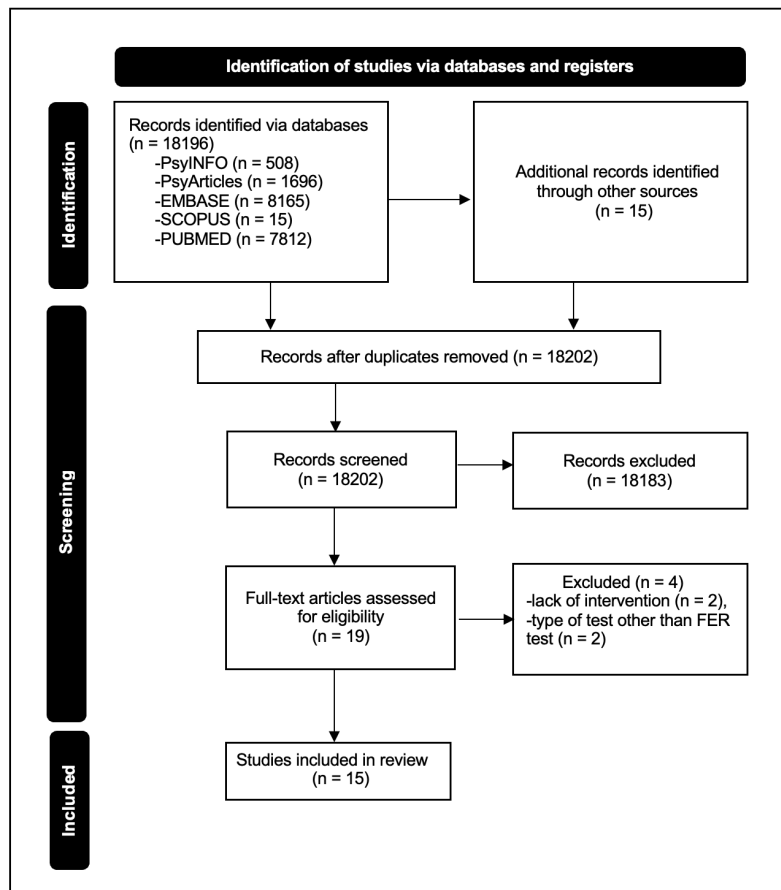


FIGURE 1. PRISMA flow diagram of the selection procedure. **PRISMA** = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Statistical Analysis

We performed all of the statistical analyses using R software version 3.6.2 and the Metafor package (Viechtbauer, 2010). Effect sizes (standard mean differences [SMD]) were weighted by the random-effects model (restricted maximum-likelihood estimator) because it is used for an unbiased estimation. The heterogeneity of intervention effects was quantified using

I^2 and Q tests. An estimate of between-study variance, tau squared (τ^2), was used as a measure of the magnitude of heterogeneity in the random-effects model. Potential publication bias was assessed using the Egger regression test. Funnel plots were analyzed, in the case of a significant Egger test, to see a small study effect. A fail-safe N test was also performed. This test calculates the number of additional studies with zero effect that would be required to give a P value > 0.05 for the pooled effect estimate.

Meta-regression analyses for the relationship between the effects of FER intervention, age, sex (ratio of females in male patient group), and Mini-Mental State Examination (MMSE; Folstein et al, 1975) score were conducted with a random-effects model using the REML (restricted maximum-likelihood estimator) method with a significance level set at $P < 0.05$. Education level could not be analyzed with these variables because of the effect size of the number of parameters to be estimated compared with the number of observations.

Risk-of-Bias Assessment

Our review includes both randomized and nonrandomized studies. We applied the RoB-2 (Risk of Bias-2; Sterne et al, 2019) tool to assess the risk of bias for all of the randomized-controlled studies. The studies were evaluated in five domains of bias—(a) bias arising from the randomization process, (b) bias due to deviations from intended interventions, (c) bias due to missing outcome data, (d) bias in measurement of the outcome, and (e) bias in selection of the reported result—as well as overall bias.

We applied the ROBINS-I (Risk Of Bias In Nonrandomised Studies of Interventions; Sterne et al, 2016) tool to assess the risk of bias for all of the nonrandomized studies. The studies were evaluated in seven domains of bias—(a) bias due to confounding, (b) bias in selection of participants into the study, (c) bias in classification of interventions, (d) bias due to deviations from intended interventions, (e) bias due to missing data, (f) bias in measurement of outcomes, and (g) bias in selection of the reported result—as well as overall bias. We created traffic light

plots to summarize the risk of bias across domains using the Risk-of-bias VISualization web application (McGuinness and Higgins, 2020).

After our assessment of the risk of bias, we graded the studies in terms of their level of evidence and recommendation according to the Oxford Center for Evidence Based Medicine. Based (n.d.) on the potential for bias relevant to the study design, this approach allowed us to assess the internal validity of a body of evidence (Sargeant et al, 2022).

More details on the study protocol are presented in supplementary material 2.

3.RESULTS

Search Results

We included 15 articles in our systematic review. A detailed description of each of the 15 studies is provided in Table 1 (Aiello et al, 2014 ; Albuquerque et al, 2014; Benussi et al, 2020; Dan et al, 2019; Enrici et al, 2017; García-Casal, Goñi-Imizcoz, et al, 2017; Jesso et al, 2011; Kempnich et al, 2017; Labuschagne et al, 2013; McIntosh et al, 2015; Mermillod et al, 2014; Mondillon et al, 2012; Péron et al, 2010; Polet et al, 2021; Wagenbreth et al, 2019).

Six of the articles were randomized-controlled studies (Benussi et al, 2020; Dan et al, 2019; Jesso et al, 2011; Kempnich et al, 2017; McIntosh et al, 2015; Polet et al, 2021), one was a pseudorandomized-noncontrolled study (Wagenbreth et al, 2019), seven were nonrandomized-controlled studies (Aiello et al, 2014; Enrici et al, 2017; García-Casal, Goñi-Imizcoz, et al, 2017; Labuschagne et al, 2013; Mermillod et al, 2014; Mondillon et al, 2012; Péron et al, 2010), and one was a nonrandomized-noncontrolled trial (Albuquerque et al, 2014). Nine of the studies were interventional (Aiello et al, 2014; Benussi et al, 2020; Dan et al, 2019; Jesso et al, 2011; Kempnich et al, 2017; McIntosh et al, 2015; Mermillod et al, 2014; Mondillon et al, 2012; Polet et al, 2021); six were noninterventional (Albuquerque et al, 2014; Enrici et al, 2017; García-Casal, Goñi-Imizcoz, et al, 2017; Labuschagne et al, 2013; Péron et al, 2010; Wagenbreth et al, 2019).

TABLE 1. Characteristics of the 15 Included Studies

Study	Sample	Type of Approach (Intervention)	FER Assessment	Time of Assessment	Intervention Condition	Outcome
García-Casal, Goñi-Iñiguez et al (2017)	32 AD	Cognitive (TAR)	Affect GRADIOR	(T0) baseline, (T1) end of sessions, (T2) +1 month	Group TAR (n = 11) Group CST (n = 11) Group control (n = 10)	(T1) total, disgust, surprise, neutral ▲/(T2) scores ● (T1) total ● (T1) scores ▼, processing speed & sadness ▼ (T1) total ▲, sadness ▲ (T1) total ● (T1) scores & processing speed total, fear, sadness, neutral ▲/(T2) total ● (T1) total ● (T1) total ●
Kempnich et al (2017)	20 HD	Cognitive (METT)	K-DEF	(T0) baseline, (T1) +6–8 weeks	Group METT (n = 10) Group control (n = 9)	(T1) total ▲, sadness ▲ (T1) total ● (T1) scores & processing speed total, fear, sadness, neutral ▲/(T2) total ● (T1) total ● (T1) total ●
Polet et al (2021)	8 AD	Cognitive (TAR)	Ekman Faces	(T0) baseline, (T1) end of sessions, (T2) +1 month	Group TAR (n = 4) Group CST (n = 4) Pre (vs) post surgery	(T1) total ● (T1) total ●
Albuquerque et al (2014)	30 PD	Neurostimulation (STN-DBS)	CATS Faces	(T0) baseline, (T1) +1 year post surgery	Group pre bvFTD (n = 15/sham [vs] real stim) Group bvFTD (n = 55/sham [vs] real stim)	(real stim): (T1) total ▲/(T3–T4) total ● (T1) total ● (T1) total ●
Benussi et al (2020)	70 FTD (bvFTD or PPA)	Neurostimulation (tDCS)	Ekman Faces	(T0) baseline, (T1) end of Stim sessions, (T3) +3 months, (T4) +6 months	Group Med ON–Stim ON: (T1) post surgery at +6 months Group control (Med ON): n/a	(real stim): (T1) total ▲/(T3–T4) total ● (T1) total ● total ●
Enrici et al (2017)	58 PD; 20 HC	Neurostimulation (STN-DBS)	Ekman Faces	Group STN-DBS: (T0) 3 months pre surgery, (T1) 3 months post surgery Group control: (T0) 3 months before APO, (T1) +3 months	Group STN-DBS (n = 24) Group control (n = 20)	(T1) total ▼, fear, sadness ▼ (T1) total ●, happiness ▲
Péron et al (2010)	44 PD	Neurostimulation (STN-DBS)	Ekman Faces	Group STN-DBS: (T0) 3 months pre surgery, (T1) 3 months post surgery Group control: (T0) 3 months before APO, (T1) +3 months	Group STN-DBS (n = 24) Group control (n = 20)	(T1) total ▼, fear, sadness ▼ (T1) total ●, happiness ▲
Wagenbreth et al (2019)	14 PD	Neurostimulation (STN-DBS)	Ekman Faces	T1: +3 to 77 months post surgery	Group Stim ON (vs) Stim OFF	(T1) fear ▲, disgust ▼
Dan et al (2019)	24 PD; 32 HC	Pharmacological (L-dopa)	Emotional face-matching task	n/a	Group Med ON Group Med OFF	total ▲ total ▼
Jesso et al (2011)	20 bvFTD	Pharmacological (Oxytocin)	NimStim set of facial expressions	(T0) baseline, (T1) 20 min after treatment, (T2) +1 week	Group oxytocin Group placebo	(T1) anger ▼, fear ▼/(T2) total ● (T1) total ●
Labuschagne et al (2013)	113 early HD; 115 pre-HD; 116 HC	Pharmacological (SSRI/Neuroleptics)	Ekman Faces	(T0) baseline	In preHD sample: Group SSRI (n = 40) Group neuroleptic (n = 29)	total ▲ total ▼ (T0) total ● (T1) total ●, disgust ▼ (T1) disgust ▲, fear ▼, sadness ▼ total ● total ●
Aiello et al (2014)	12 PD; 13 HC	Neurostimulation + Pharmacological (STN-DBS/L-dopa)	NimStim set of facial expressions	(T0) pre surgery, (T1) 5 days after for Stim OFF, or, 2–6 months after for Stim ON	Pre surgery: Group Med ON (vs) Med OFF Post surgery: Group Med ON–Stim ON Group Med ON (vs) OFF Group Med ON (vs) Med ON–Stim ON	(T1) total ●, disgust ▼ (T1) disgust ▲, fear ▼, sadness ▼ total ● total ●
McIntosh et al (2015)	16 early PD; 21 HVC; 23 HC	Neurostimulation + Pharmacological (STN-DBS/ODT)	TASIT	n/a	Group Med ON (vs) Med ON–Stim ON	total ● total ●
Mermillod et al (2014)	14 PD; 14 HC	Neurostimulation + Pharmacological (STN-DBS/DRT)	Ekman Faces	(T1) at least 6 months post surgery	Group Med ON: Stim ON (vs) Stim OFF Group Med OFF: Stim ON (vs) Stim OFF	total ● total ●
Mondillon et al (2012)	14 PD; 14 HC	Neurostimulation + Pharmacological (STN-DBS/L-dopa)	K-DEF	(T1) at least 6 months post surgery	Group Med ON: Stim ON Group Med OFF: Stim ON Group Med OFF: Stim OFF	total ▲ disgust ▼ fear ▼

▲ = significant improvement in performance. ▼ = significant deterioration of performance. ● = no significant change in performance. AD = Alzheimer disease. APO = continuous subcutaneous infusion of apomorphine (for L-dopa-resistant patients). CATS = Comprehensive Affect Testing System. CST = cognitive stimulation therapy. DRT = dopamine replacement therapy. bvFTD = behavioral variant of frontotemporal dementia. FER = facial emotion recognition. HC = healthy controls. HVC = healthy young controls. HD = Huntington disease. K-DEF = Karolinska-Directed Emotional Faces. L-dopa = Levodopa. METT = micro expressions training tool. Med = Medication. ODT = optimal drug therapy. PD = Parkinson disease. PPA = primary progressive aphasia. Pre-HD = Presymptomatic Huntington disease. STN-DBS = subthalamic nucleus deep brain stimulation. sham = inactive stimulation (condition control). Stim = stimulation. SSRI = selective serotonin reuptake inhibitor. TASIT = The Awareness of Social Inference Test. TAR = training on affect recognition. tDCS = transcranial deep current stimulation.

For the meta-analysis, we contacted the authors of articles that did not provide sufficient data to calculate effect sizes. Only two authors responded to this question. Intergroup comparisons were excluded from the calculation of effect sizes, and seven articles were included in the meta-analysis part (Benussi et al, 2020; Enrici et al, 2017; García-Casal, Goñi-Imizcoz, et al, 2017; Kempnich et al, 2017; McIntosh et al, 2015; Péron et al, 2010; Polet et al, 2021). Some articles, owing to experimental conditions, were considered separate studies (Benussi et al, 2020; García-Casal, Goñi-Imizcoz, et al, 2017; McIntosh et al, 2015).

Type of Disease

Across all of the studies considered, there was a total of 604 individuals with a diagnosis of either AD (two studies), HD (two studies), bvFTD (two studies), or PD (nine studies).

Assessment of FER Ability

The 15 studies used various methods (ie, different sets of facial images) to assess FER ability. Pictures from Ekman's Faces set (Ekman and Friesen, 1976) were used the most frequently to investigate FER ability (seven studies). Other studies used the following tests: Affect GRADIOR (García-Casal, Vanova, et al, 2017), Karolinska-Directed Emotional Faces (Lundqvist et al, 1998), Comprehensive Affect Testing System (Froming et al, 2006), NimStim set of facial expressions (Tottenham et al, 2009), Emotion Evaluation subtest of the Awareness of Social Inference Test (McDonald et al, 2003), and emotional face-matching task (Hariri et al, 2002).

Twelve of the 15 studies assessed the six basic emotions (joy, fear, disgust, sadness, surprise, and anger). Other studies assessed fewer basic emotions, such as only anger and fear (Dan et al, 2019); fear, disgust, and happiness (Wagenbreth et al, 2019); and fear, happiness, sadness, and anger (Jesso et al, 2011).

Overall Efficacy of the Interventions on FER Ability

Our meta-analysis resulted in a significant large effect size for FER improvement in individuals with NDD by the interventions pooled together (SMD: 1.21, 95% CI = 0.11, 2.31, $z = 2.15$, $P = 0.03$; Figure 2). Considerable heterogeneity was observed ($Q = 92.41$, $df = 9$, $P = 0.0001$). The Egger regression test showed no evidence of publication bias for the overall effects of the FER ability interventions ($b = -1.42$, $SE = 1.71$, $P = 0.10$), and the fail-safe N value was 140 (Table 2).

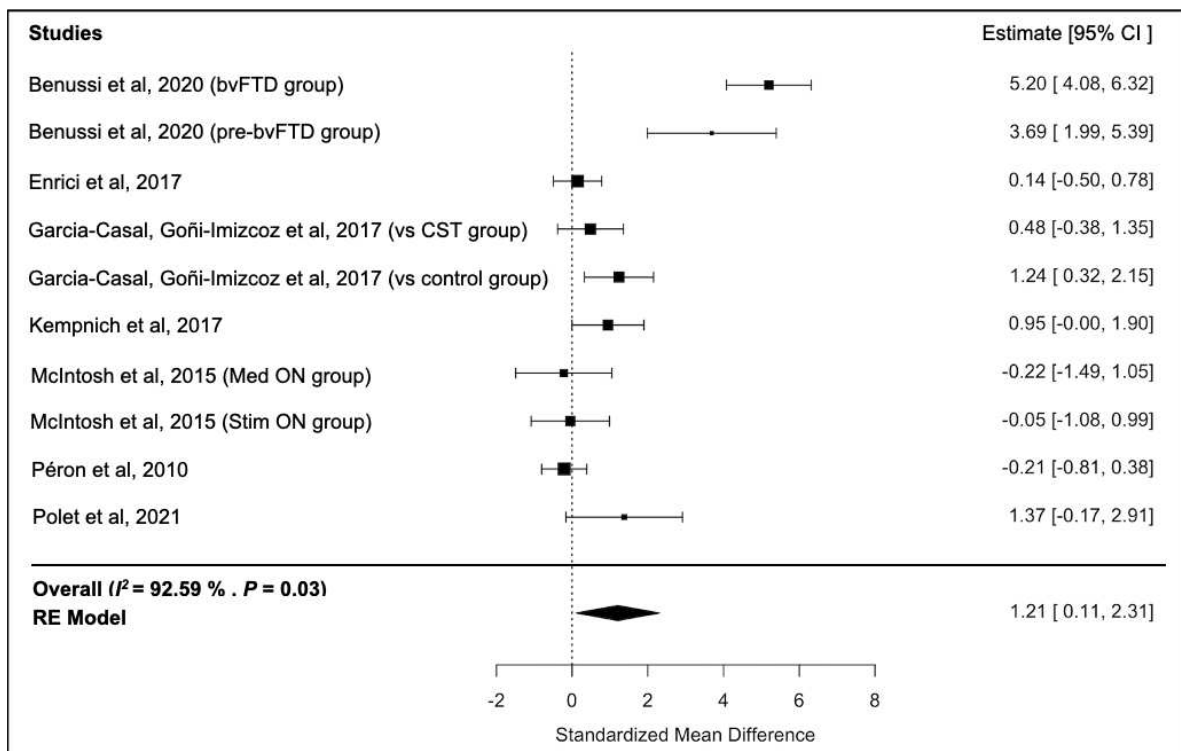


FIGURE 2. Forest plot of the overall intervention approaches with FER as the outcome variable. **bvFTD** = behavioral variant of frontotemporal dementia. **CST** = cognitive stimulation therapy. **FER** = facial emotion recognition. **RE** = random effects.

TABLE 2. Sample Size, Standardized Mean Difference, Test Statistics, Heterogeneity, and Fail-safe Number of Studies Included

Type of approach	n	Ni	Nc	SMD	95% CI	z	P	Q test P	τ^2	I^2	Nfs
Overall	7	138	109	1.21	0.11–2.31	2.15	0.03	<0.0001	2.83	92.59%	140
Cognitive	3	35	35	0.93	0.43–1.42	3.65	0.0003	0.62	0	0%	17
Neurostimulation	5	97	70	1.70	-0.50–3.90	1.51	0.12	<0.0001	5.98	96.79%	58

n = number of studies. **Nc** = sample of the control group. **Nfs** = fail-safe number from Rosenthal. **Ni** = sample of the intervention group. **SMD** = standardized mean difference.

The meta-regression analyses indicated an effect of sex on the interventions, with greater benefit for females ($b = 2.93$, $SE = 0.82$, $z = 3.56$, $P = 0.0004$). None of the other variables (age and MMSE score) showed a significant association with FER intervention improvement.

In total, three different intervention approaches for FER improvement were found in this meta-analysis: cognitive approach, with two different types of intervention (TAR, METT); neurostimulation approach, with two different types of intervention (tDCS and STN-DBS); and pharmacological approach, with four different types of intervention (oxytocin, SSRI, neuroleptic, L-dopa); as well as an approach that combined neurostimulation and pharmacological interventions.

Efficacy of the Cognitive Interventions on FER Ability

The cognitive interventions had a significant large effect size for FER improvement in individuals with NDD (SMD: 0.93, 95% CI = 0.43, 1.42, $z = 3.65$, $P = 0.0003$; Figure 3). However, the results showed a high level of heterogeneity ($Q = 1.76$, $df = 3$, $P = 0.62$). The Egger regression test showed no evidence of publication bias for the cognitive interventions ($b = 0.01$, $SE = 1.57$, $P = 0.47$), and the fail-safe N value was 17 (Table 2).

More specifically, a significant improvement in FER ability was shown for the TAR program in individuals with AD. The recognition of disgusted, surprised, and neutral faces (García-Casal, Goñi-Imizcoz, et al, 2017) and of fearful, sad, and neutral faces (Polet et al, 2021) improved significantly. The latter study examined the link between improvement in FER ability, BPSD, and caregiver burden. The authors found that FER ability improvement correlated with a decrease in BPSD and caregiver burden. FER ability was also improved in individuals with pre- and early symptomatic HD with the METT intervention, especially for sadness recognition (Kempnich et al, 2017).

Follow-up assessment of the individuals with AD after the TAR program showed that the improvement in FER ability lasted 1 month post intervention (García-Casal, Goñi-Imizcoz, et al, 2017; Polet et al, 2021).

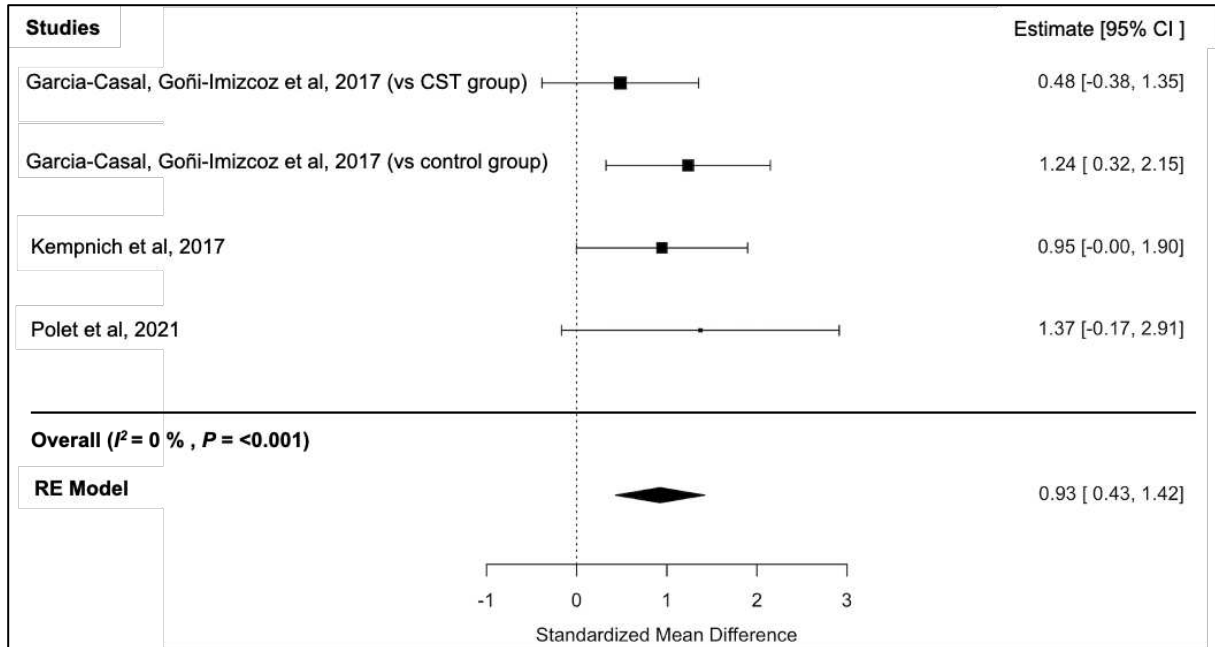


FIGURE 3. Forest plot of the cognitive approach to intervention with FER as the outcome variable. **CI** = Confident Interval. **FER** = facial emotion recognition. **RE** = random effects

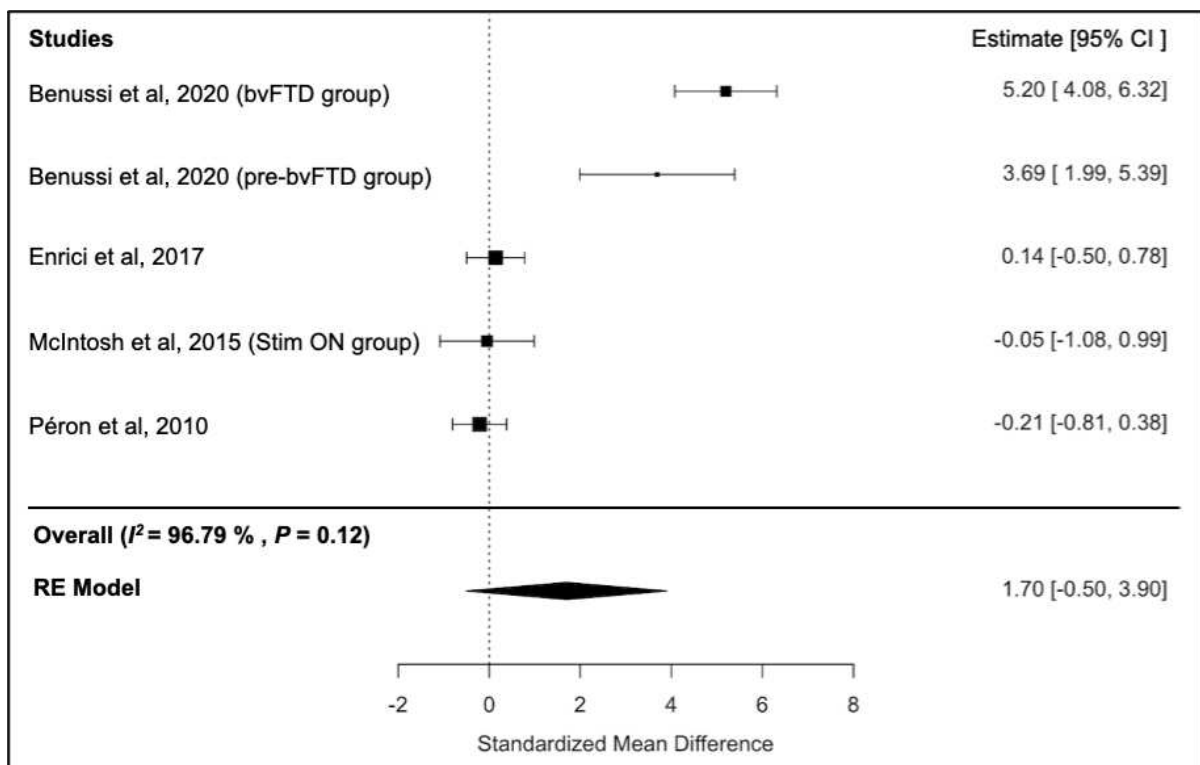


FIGURE 4. Forest plot of the neurostimulation approach to intervention with FER as the outcome variable. **CI** = Confident Interval. **FER** = facial emotion recognition. **RE** = random effects.

Efficacy of the Neurostimulation Interventions on FER Ability

The neurostimulation interventions had a large and nonsignificant effect size for FER improvement in individuals with NDD (SMD: 1.70, 95% CI = -0.50, 3.90, $z = 1.84$, $P = 0.12$; Figure 4). However, the results showed considerable heterogeneity ($Q = 5.98$, $df = 4$, $P = 0.0001$). The Egger regression test showed no evidence of publication bias for the neurostimulation interventions ($b = -2.23$, $SE = 6.21$, $P = 0.09$), and the fail-safe N value was 58 (Table 2).

More specifically, a significant improvement in FER ability was shown for anodal tDCS in both bvFTD groups (presymptomatic and symptomatic), with a decrease in BPSD (Benussi et al, 2020). A significant improvement in fear recognition was shown for STN-DBS in the individuals with PD (Wagenbreth et al, 2019). Conversely, a decrease in disgust recognition was found following STN-DBS in the individuals with PD (Wagenbreth et al, 2019). Moreover, a significant negative effect for fear and sadness recognition after STN-DBS in PD was found (Péron et al, 2010). A lack of effect of STN-DBS on FER ability in individuals with PD was reported in two articles (Albuquerque et al, 2014; Enrici et al, 2017).

Only one study conducted follow-up assessments at 3 and 6 months post intervention (Benussi et al, 2020). This study showed that the improvement by anodal tDCS in the bvFTD group was maintained even at 6 months post intervention.

Efficacy of the Pharmacological Interventions on FER Ability

Due to a lack of sufficient data, the effect size for pharmacological interventions could not be calculated. However, the literature review showed that an improvement in FER ability was observed with SSRI intervention in individuals with HD (Labuschagne et al, 2013). Dan et al (2019) found an improvement in FER ability in individuals with PD after using L-dopa. In contrast, two studies (Aiello et al, 2014; McIntosh et al, 2015) showed no effect of dopaminergic

therapy on individuals with PD. A deleterious effect of neuroleptics on FER ability was observed in individuals with HD (Labuschagne et al, 2013). A decrease in the recognition of anger and fear was observed in individuals with bvFTD due to oxytocin (Jesso et al, 2011). This study also showed an improvement in BPSD 8 hours after intranasal oxytocin administration.

Only one study conducted a follow-up assessment of pharmacological interventions (Jesso et al, 2011). This study showed that the effects of oxytocin were not maintained at 1 week post intervention in individuals with bvFTD.

Efficacy of the Combined Interventions on FER Ability

Interventions combining neurostimulation (STN-DBS) and pharmacological interventions were studied only among individuals with PD (Aiello et al, 2014; McIntosh et al, 2015; Mermillod et al, 2014; Mondillon et al, 2012). The study by Mondillon et al (2012) showed an improvement in FER ability using a combination of STN-DBS and L-dopa, whereas the three other studies showed no beneficial effect (Aiello et al, 2014; McIntosh et al, 2015; Mermillod et al, 2014).

Only one study (Aiello et al, 2014) conducted a follow-up assessment of the combination of STN-DBS and L-dopa. This study showed no significant change in the effect on individuals with PD at 2–6 months post intervention.

Risk-of-Bias Assessment

All of the randomized studies were found to have an overall high risk of bias (Benussi et al, 2020; Dan et al, 2019; Jesso et al, 2011; Kempnich et al, 2017; McIntosh et al, 2015; Polet et al, 2021; Wagenbreth et al, 2019) (supplemanrty material 3, Figures S1–S4). Concerns of bias were most common for domains 2 (corresponding to bias in deviations from the intended interventions) and 4 (corresponding to bias in measurement of the outcome), and all of the

assessed studies had a high risk of bias for domain 5 (corresponding to bias in selection of the reported result).

We also found an overall serious risk of overall bias for seven of the eight nonrandomized studies (Aiello et al, 2014; Albuquerque et al, 2014; Enrici et al, 2017; Labuschagne et al, 2013; Mermillod et al, 2014; Mondillon et al, 2012; Péron et al, 2010). In one study, the overall risk of bias was deemed critical (García-Casal, Goñi-Imizcoz, et al, 2017) (SDC 3, Figures S5 and S6; Ttile 9).

According to the level of evidence of the Oxford Center for Evidence Based Medicine (n.d.), the randomized studies had an evidence level of 1B (ie, the evidence was superior compared to other study designs), and the nonrandomized studies had an evidence level of 2B (ie, individual cohort study or low-quality randomized controlled study) (Supplemenatry Material 7b). In terms of grades of recommendation, the studies that were classified as having a consistent level of evidence were considered to have fair research-based evidence to support the recommendation.

4.DISCUSSION

To our knowledge, this systematic review is the first to include a meta-analysis of several types of interventions for improving FER ability in individuals with various NDDs. Our results showed that three main approaches to intervention were used to improve FER ability in individuals with NDD: cognitive, neurostimulation, and pharmacological. These included single or combined interventions (neurostimulation with pharmacological).

The current meta-analysis provides evidence that FER impairment in individuals with NDD can be improved by a variety of interventions, with a large effect size of overall FER-targeted interventions. The cognitive approaches were the most effective in improving FER ability, with a large and significant effect size. The effect size of the neurostimulation approaches was large, but not statistically significant. Pharmacological interventions were

beneficial, except for neuroleptics and oxytocin. Whatever the type of approach, when there was an improvement of FER, the improvement was often maintained over time and was associated with a decrease in BPSD and caregiver burden.

Cognitive Approaches to Improving FER Ability

The finding that cognitive interventions had a large effect on the improvement of FER ability in individuals with AD and those with HD may be surprising given the degenerative characteristics of AD and HD and the presence of memory impairments. Nonetheless, these interventions (ie, TAR, METT) use techniques such as error-less learning (Clare et al, 2003) and spaced retrieval (Camp et al, 1996), which have proven their effectiveness in individuals with NDD.

It is important to note that FER requires eye-gaze strategies. FER ability is mainly related to observation of the eye area, except for the recognition of joy and disgust, which is more related to observation of the mouth area (Guarnera et al, 2017; Schurgin et al, 2014). In AD, in which the recognition of negative facial emotions is impaired (Fernández-Ríos et al, 2021), observation of the eye area is diminished (Ogrocki et al, 2000; Polet et al, 2017, 2021, 2022). However, individuals with AD were able to recognize fear when attention was guided to the eyes (Hot et al, 2013), and FER ability was improved when the emotional salience of the faces was increased (recognition of high intensity emotions) (Phillips et al, 2010), suggesting attentional origin to FER impairment.

Moreover, FER improvement in individuals with AD after the TAR program was associated with a modification of their eye-gaze strategies, with increased observation of the nose and eye area (Polet et al, 2021). One hypothesis might be that cognitive interventions alter these atypical gazing strategies by drawing attention to emotionally salient areas of the face during FER for each basic facial expression. Furthermore, some studies have concluded that

nonpharmacological interventions' effects can exceed the effects of symptomatic pharmacological interventions (Hempel et al, 2010; Herholz et al, 2013).

Neurostimulation Approaches to Improving FER Ability

The improvement in FER ability by neurostimulation interventions was large but not statistically significant. Another recent meta-analysis concluded that noninvasive brain stimulation techniques such as repetitive transcranial magnetic stimulation and tDCS had a significant beneficial effect on general cognition in individuals with AD and those with mild cognitive impairment (Teselink et al, 2021). Regarding these results and our conclusions, we can argue that cognitive domains can be improved even when no improvement in FER ability is gained from noninvasive brain stimulation.

In our review, only one study used tDCS in individuals with bvFTD. This study (Benussi et al, 2020) found an improvement in FER ability accompanied by a decrease in BPSD, with the maintenance of performance even 6 months post intervention. This is the only study that assessed FER ability in individuals with bvFTD after a long-term period (Benussi et al, 2020) and seems an interesting lead for this disease wherein BPSD is at the forefront.

In individuals with PD, we noted a deleterious and/or non-effect of STN-DBS. These results are in line with a critical review (Kalampokini et al, 2020) that reported that the worse performance could be explained by a direct effect of DBS on STN or by the disruption of STN connections with the basal ganglia or cortical areas that are implicated in FER ability after surgery. This disruption could also be affected by the inhibition of STN by DBS. Moreover, the basal ganglia are involved in FER ability (Gothwal et al, 2022) and have been affected by dopaminergic loss in individuals with PD.

Neurophysiological studies have explained the worsening of FER ability through the modulation of STN oscillatory activity (Bronte-Stewart et al, 2009; Giannicola et al, 2010;

Kühn et al, 2008; Rossi et al, 2008). The emerging role of low-frequency alpha and beta oscillations in the STN in individuals with PD is not only motor (Accolla et al, 2016) but might also be involved in emotional information processing (Marceglia et al, 2011).

One STN-DBS study (Aiello et al, 2014) found an improvement in disgust recognition and a worsening recognition of sadness and fear immediately after DBS implant surgery and before turning stimulation on in individuals with PD. The authors described it as a *microlesion effect* that was present after surgery, which could have an impact on the recognition of single emotions due to metabolic changes in cerebral regions such as the STN, thalamus, pallidum, and sensorimotor cortex (Hilker et al, 2008; Pourfar et al, 2009).

Modification of glucose metabolism or regional blood flow after STN-DBS surgery in areas implicated in FER processing has already been demonstrated in many studies (Kalampokini et al, 2020). In these neuroimaging studies, it has been suggested that modifications in the cerebral metabolism of the striatal-thalamo-cortical circuits might be induced by STN-DBS surgery, involving the orbitofrontal and anterior cingulate cortex, or might modulate a frontal network that is linked to the limbic and associative STN territories (Kalampokini et al, 2020).

Pharmacological Approaches to Improving FER Ability

The pharmacological interventions resulted in mixed results. For example, dopaminergic therapy had a beneficial effect on individuals with PD (Dan et al, 2019). FER impairments might be explained by neural changes in several areas of the brain as well as by altered dopamine transmission in the mesocorticolimbic system (Argaud et al, 2018), which includes regions such as the orbitofrontal cortex and amygdala, whose presynaptic dopaminergic functioning is impaired from the early stages of PD (Ouchi et al, 1999). This dysfunction at the amygdalar level leads to behavioral consequences (Diederich et al, 2016). Dopamine might

induce hyperactivity of the amygdala, leading to an overdose effect on FER ability, and compensatory mechanisms might occur (Argaud et al, 2018).

Oxytocin had a deleterious effect on the recognition of negative emotions (anger and fear) in individuals with bvFTD (Jesso et al, 2011). Several studies have proven that oxytocin is a crucial hormone for limbic system function (eg, Insel and Young, 2000), wherein the amygdalo-hippocampal junction has a key role in the implicit recognition of emotions (Critchley et al, 2000).

The use of SSRIs improved FER ability in individuals with presymptomatic HD (Labuschagne et al, 2013). This outcome is in line with a study that was conducted on individuals with bipolar disorder (Vierck et al, 2015). Conversely, other studies have found no effect of antidepressant medication on FER processing (Martino et al, 2011; Samamé et al., 2015).

A deleterious effect of atypical neuroleptics was observed in individuals with presymptomatic HD (Labuschagne et al, 2013). Conversely, in individuals with schizophrenia, FER ability was found to improve using typical (Hempel et al, 2010) or atypical (Behere et al, 2009) neuroleptics. All types of neuroleptics affect dopamine regulation in the mesocorticolimbic system, which might lead to better regulation of amygdala activity and emotion regulation (Salgado-Pineda et al, 2005).

A study by Williams et al (2003) highlighted atypical visual scanning during FER in individuals with schizophrenia, similar to what was seen here in individuals with NDD (Polet et al, 2017, 2021, 2022). Williams et al (2003) also found that individuals with schizophrenia with atypical neuroleptic treatment allocated as much attention to salient features of the face (eyes, nose, and mouth) as controls, whereas typical neuroleptic treatment led to fewer observations of these features.

Combined Approaches to Improving FER Ability

Only one study indicated a beneficial effect of STN-DBS combined with L-dopa on FER ability (Mondillon et al, 2012). No other studies found any impact of combined interventions on FER ability. In the combination of STN-DBS and dopaminergic therapy, it is uncertain whether there is an effective medication for the ON condition due to dopaminergic fluctuations (Péron et al, 2013). In addition, a recent critical review indicated a methodological bias in protocols that combine STN-DBS and dopaminergic therapy. Patients were not taking their usual treatment (Kalampokini et al, 2020). In light of our positive results concerning the cognitive approach, and the positive results obtained with certain molecules in NDD according to the literature review, it would be interesting to evaluate the effects of a combination of these two types of approaches on FER ability in individuals with NDD.

FER Interventions According to NDD

In our review, most of the studies investigating the use of intervention to improve FER ability in individuals with NDD were conducted on individuals with PD (nine studies) (Aiello et al, 2014; Albuquerque et al, 2014; Dan et al, 2019; Enrici et al, 2017; McIntosh et al, 2015; Mermillod et al, 2014; Mondillon et al, 2012; Péron et al, 2010; Wagenbreth et al, 2019). Although bvFTD is the pathology that is most affected by social cognition deficits, only two studies in our review included individuals with bvFTD. The study by Benussi et al (2020) used a neurostimulation intervention, tDCS, to improve FER ability and obtained a beneficial effect. In contrast, the study by Jesso et al (2011) used a pharmacological intervention and obtained a deleterious effect.

In individuals with HD, cognitive and pharmacological interventions were used in two distinct studies (Kempnich et al, 2017; Labuschagne et al, 2013), whereas in individuals with AD, only cognitive interventions (especially TAR intervention) were used in two studies

(García-Casal, Goñi-Imizcoz, et al, 2017; Polet et al, 2021). No study has been found on Lewy body dementia because it has an altered temporo-occipital cortex that is implicated in FER processing. To conclude, neurostimulation (nine studies) (Aiello et al, 2014; Albuquerque et al, 2014; Bennusi et al, 2020; Enrici et al, 2017; McIntosh et al, 2015; Mermillod et al, 2014; Mondillon et al, 2012; Péron et al, 2010; Wagenbreth et al, 2019) and pharmacological (seven studies) (Aiello et al, 2014; Dan et al, 2019; Jesso et al, 2011; Labuschagne et al, 2013; McIntosh et al, 2015; Mermillod et al, 2014; Mondillon et al, 2012) approaches are the most studied to improve FER ability in individuals with NDD.

Additional Findings

To explore the possible relationship between the effect of FER-targeted interventions in individuals with NDD and age, sex, and MMSE score, we conducted a meta-regression analysis. Only sex had a significant relationship with FER improvement in individuals with NDD. This result is consistent with a study by Olderbak et al (2019) that found higher FER ability in females compared with males; this difference is present since childhood (McClure, 2000) and persists in the elderly (Abbruzzese et al, 2019). Therefore, our findings should be cautiously interpreted. We could not analyze the relationship between the effect of FER-targeted interventions in individuals with NDD and age, sex, MMSE score, and education level.

Only four of the 15 studies in our review conducted a follow-up assessment. Three of them showed postintervention maintenance of performance but did not exceed 6 months. Although the follow-up assessment period may seem short (6 months) considering the degenerative feature of these diseases. However, long-term studies are necessary.

BPSD and Caregiver Burden

It is well established in the literature that poor social cognition is associated with BPSD and, consequently, a marked caregiver burden in NDD (Giguère-Rancourt et al, 2021; Polet et al, 2017, 2021, 2022). In this review, only three of the 15 studies considered either BPSD or caregiver burden. Interestingly, these studies used three different intervention approaches. We suggest that the improvement in FER ability due to any type of intervention approach may lead to a decrease in BPSD in individuals with bvFTD and those with AD (Benussi et al, 2020; Jesso et al, 2011; Polet et al, 2021), as well as to a decrease in caregiver burden for caregivers of individuals with AD (Polet et al, 2021).

Social cognition abilities cannot be considered as isolated abilities; they involve other cognitive abilities such as episodic and working memory or executive functions (Stone and Gerrans, 2006). A study by Virtanen et al (2017) showed that the ability to recognize facial emotions decreased during normal aging, correlating with cognitive decline in general. A relationship exists between cognitive decline, social cognition impairments, and caregiver burden. Because of the cognitive impairments, the individual needs to be supervised by his or her principal caregiver, which leads to a cognitive dependence, resulting in caregiver burden (Allen et al, 2019; Kim et al, 2012).

The literature has already pointed out a relationship between social cognition impairments, BPSD, and caregiver burden in individuals with NDD (Gregory et al, 2002; Ibañez and Manes, 2012; Kempnich et al, 2018; Polet et al, 2017, 2021; 2022; Martinez et al, 2018; Santamaría-García et al, 2016; Shimokawa et al, 2001; Torralva et al, 2009). Thus, following the beneficial effects of interventions on FER ability and their potential positive repercussions on patients' cognitive abilities, BPSD, and family caregiver burden, it is likely that this type of intervention could improve the quality of life of the patient/family caregiver couple (Carton et al, 1999; Hofer et al, 2009; Janssens et al, 2012; Kordsachia et al, 2017;

Kornreich et al, 2002). We suggest that among all of the identified approaches, the cognitive approach could be offered as a priority to individuals with NDD because the interventions of this approach are more effective, without any side effect (Herholz et al, 2013). Moreover, the cognitive interventions are inexpensive and more accessible than the other types.

Review Strengths and Limitations

The strength of this study is that it is the first systematic review and meta-analysis to analyze different types of interventions targeting FER ability improvement in individuals with NDD. Additionally, our meta-analysis had a large failure-safe N value, and here was no evidence of publication bias when we performed different meta-analyses for the different types of intervention approaches. Plus, all of the intervention groups were compared with a matched control group in each study.

However, our review does have several limitations. First, there was considerable heterogeneity of intervention effects from the included studies, which might be explained by differences in patient samples, intervention types, and control groups. Then, for the meta-regression analysis, it was not possible to study the possible interactions between level of education and effectiveness of interventions because educational level and social cognition ability are correlated (Demenescu et al, 2014). Moreover, this systematic review and meta-analysis included only four types of NDD within 15 articles, with only two focusing on individuals with bvFTD. Finally, despite a lack of publication bias, a high risk of bias cannot be excluded for the included studies. However, according to the level of evidence of Oxford Center for Evidence Based Medicine (n.d.), there was a consistent level for all of the studies included in the review.

5.CONCLUSION

Our meta-analysis showed that FER ability can be improved in individuals with NDD by using a variety of intervention approaches. This improvement may lead to a decrease in BPSD and caregiver burden. As a consequence, remediation of FER ability could be useful in BPSD management of individuals with NDD. A non-pharmacological therapy would be most useful in the prevention of BPSD.

A large effect was observed for cognitive interventions, suggesting that they should be studied further for the improvement of FER ability in individuals with NDD, especially in individuals with bvFTD. It would be interesting to investigate other NDDs, such as Lewy body dementia or progressive supranuclear palsy, in terms of their association with FER impairment and BPSD.

Future studies combining these different intervention approaches, especially cognitive and pharmacological, and studying their long-term effectiveness, consequences on the family caregiver, and period of institutionalization could be interesting avenues for individuals with NDD and their caregivers to investigate.

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7. Supplementary Materials

7.1. Supplementary Material 1



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Section Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Section Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Section Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Section Objective
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Section Methods, first to third paragraph
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Section Methods, first paragraph
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Section Methods, first to second paragraph
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Section Methods, second paragraph
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Section Methods, second to third paragraph
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Section Methods, second to third paragraph
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Section Methods,



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
			third paragraph, and Section Results, third paragraph
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Section Methods, sixth to eighth paragraph
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Section Methods, fourth to fifth paragraph
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Section Methods, second paragraph Figure 1
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Section Methods, second paragraph. Section Results, third paragraph
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Section Methods, third paragraph
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Section Methods, third to fourth paragraph
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Section Methods, fourth to fifth paragraph



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Section Methods, fourth to fifth paragraph
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Section Methods, sixth to eighth paragraph Figure 1
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Section Methods, eighth paragraph
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Section Results, first to third paragraph Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Section Results, first to third paragraph Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Section Results, first to third paragraph Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Section Results, nineteenth to twentieth paragraph SDC 3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect <u>estimate</u> and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 2, 3, 4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Section Results, fourth to



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
			twentieth paragraph SDC 3
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Section Results, fourth to twentieth paragraph Figure 2, 3, 4 Table 2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Section Results, fourth to twentieth paragraph Table 2
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Section Results, twentieth paragraph SDC 3
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	SDC 3
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Section Discussion, first to twelfth paragraph
	23b	Discuss any limitations of the evidence included in the review.	Section Discussion, thirteenth paragraph
	23c	Discuss any limitations of the review processes used.	Section Discussion, thirteenth paragraph
	23d	Discuss implications of the results for practice, policy, and future research.	Section Discussion, tenth to



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
			eleventh paragraph
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	SDC 2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	SDC 2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Section title SDC 2
Competing interests	26	Declare any competing interests of review authors.	Section title SDC 2
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Section Methods, ninth paragraph

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;[372:n71](#). doi: 10.1136/bmj.n71
For more information, visit: <http://www.prisma-statement.org/>

7.2. Supplementary Material 2

Systematic review and meta-analysis protocol

General information

1. Start – End Date

26/11/2021- 19/07/2022

2. No funding/sponsors
3. No conflicts of interest
4. Review not registered

Review methods

5. Review question:

Can the ability to recognize facial emotions in patients with neurodegenerative diseases be improved?

6. Search method

This systematic review and meta-analysis were performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Page et al, 2021).

The literature search was conducted using PsycINFO, PsycArticles, EMBASE, SCOPUS and PUBMED to identify studies published between January 2011 and December 2021 using the combination of keywords: “Alzheimer's disease,” “neurodegenerative disease,” “dementia,” “remediation,” “emotion,” and “facial expressions.”

7. Studied domain

This systematic review and meta-analysis aimed to identify several types of interventions targeting the improvement of facial emotion recognition (FER) ability in neurodegenerative diseases (NDD) and to explore the duration of their effects and their possible impacts on behavioral and psychological symptoms of dementia (BPSD) and caregiver burden.

8. Studied population

Population with a neurodegenerative disease.

9. Interventions

Different types of interventions to improve facial emotion recognition ability.

10. Comparators

Control group.

11. Types of study

Randomized-controlled, non-randomized-controlled and non-randomized non-controlled studies.

For systematic review: inclusions of the studies responding to inclusion criteria.

For meta-analysis: inclusion of the studies which concern inter-comparison (intervention vs. control).

12. Outcomes

- a. to identify several types of interventions targeting the improvement of FER ability in NDD and to investigate the magnitude of their efficacy.
- b. to explore the duration of their effects and their possible impacts on BPSD and caregiver burden.

13. Data extraction

We extracted the data as (1) author and year of publication; (2) type of disease; (3) sample sizes; (4) allocation of groups (experimental vs. control); (5) type of intervention approach; (6) type of assessment; (7) outcomes measures; (8) availability of follow-up data; (9) main findings, in an Excel spreadsheet.

14. Statistical analysis

Statistical analyses were performed using R software version 3.6.2 and the Metafor package. Effect sizes (standard mean differences [SMD]) were weighted by the random effects model. The heterogeneity was quantified using I^2 and Q -tests. An estimate of between-study variance, tau squared (τ^2), was used as a measure of the magnitude of heterogeneity in the random-effects model. Publication bias was assessed using Egger's test. Funnel plots were analyzed, in the case of a significant Egger test, to see a small study effect. A fail-safe N test was also performed. Meta-regression analyses for the relationship between the effects of FER interventions, age, gender, and Mini-Mental State Examination (MMSE) scores were conducted with a random-effects model.

15. Eligibility criteria

Eligible articles were those studying interventions to improve FER in any NDD. Randomized-controlled, non-randomized-controlled and non-randomized non-controlled studies were considered. The exclusion criteria were disease other than NDD, assessment of emotion recognition other than the FER test, and lack of intervention to improve FER ability. Other than English or French articles, case studies, and review articles were excluded. For the meta-analysis, the authors of articles that did not provide sufficient data to calculate effect sizes were contacted.

16. Article screening and selection

Firstly, the titles and abstracts of papers retrieved were screened and those that were not respecting the inclusion criteria were excluded. If needed, the full text was downloaded. Three review team members independently screened the articles for eligibility.

17. Risk of bias assessment

The risk of bias assessment and visualization performed by using the RoB-2 tool (Risk of Bias-2) (Sterne et al, 2019) for randomized controlled studies, the ROBINS-I tool (Risk Of Bias In Non-randomized Studies-of Interventions) (Sterne et al, 2016) for non-randomized studies. For traffic light plots, a web app Risk-of-bias VISualization (RobVIS) was used (McGuinness & Higgins). Once the assessment of the risk of bias was done, the studies have been graded in terms of the level of evidence according to the Oxford Center for Evidence Based Medicine (OCEBM).

7.3. Supplementary Material 3

Risk of bias assessments

Per-protocol	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall		
	2	Dan et al, 2019	Inerventional	Control	improvement FER	1	+	!	-	!	-	-	+	Low risk
	3	Jesso et al, 2011	Interventional	Control	Improvement FER	1	+	+	+	+	-	-	!	Some concerns
	4	Kempnich et al, 2017	Interventional	Control	Improvement FER	1	+	-	+	!	-	-	-	High risk
	5	Polet et al, 2021	Interventional	Control	improvement FER	1	+	-	+	+	-	-	-	
	6	Wagenbreth et al, 2019	Non interventional	NA	Improvement FER	1	-	-	+	-	-	-	-	D1 Randomisation process
	7	McIntosh et al, 2015	Interventional	Control	Improvement FER	1	+	-	-	!	-	-	-	D2 Deviations from the intended interventions
														D3 Missing outcome data
														D4 Measurement of the outcome
														D5 Selection of the reported result

Figure 5: Traffic light plots for randomized and per-protocol studies.

Intention-to-treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall			
	1	Benussi et al, 2020	Interventional	Control	improvement FER	1	+	+	+	+	-	-	+	Low risk	
														!	Some concerns
														-	High risk

Figure 6: Traffic light plots for randomized and intention-to-treat studies.

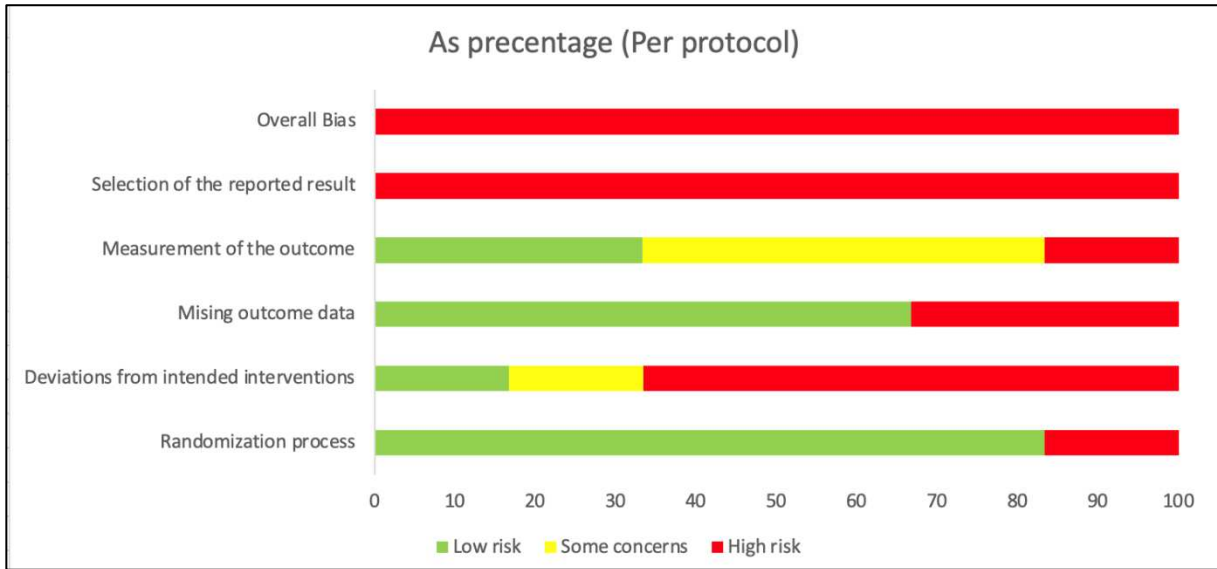


Figure 7: Plot of the percentage of risk of bias assessment at each level of risk of bias per domain for randomized and per-protocol studies

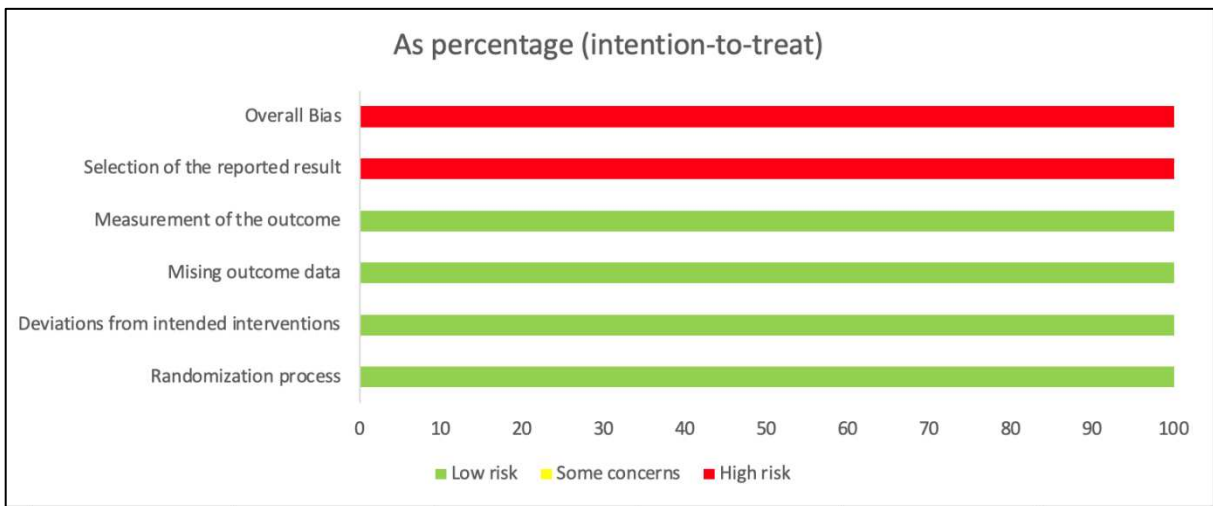


Figure 8: Plot of the percentage of risk of bias assessment at each level of risk of bias per domain for randomized and intention-to-treat studies

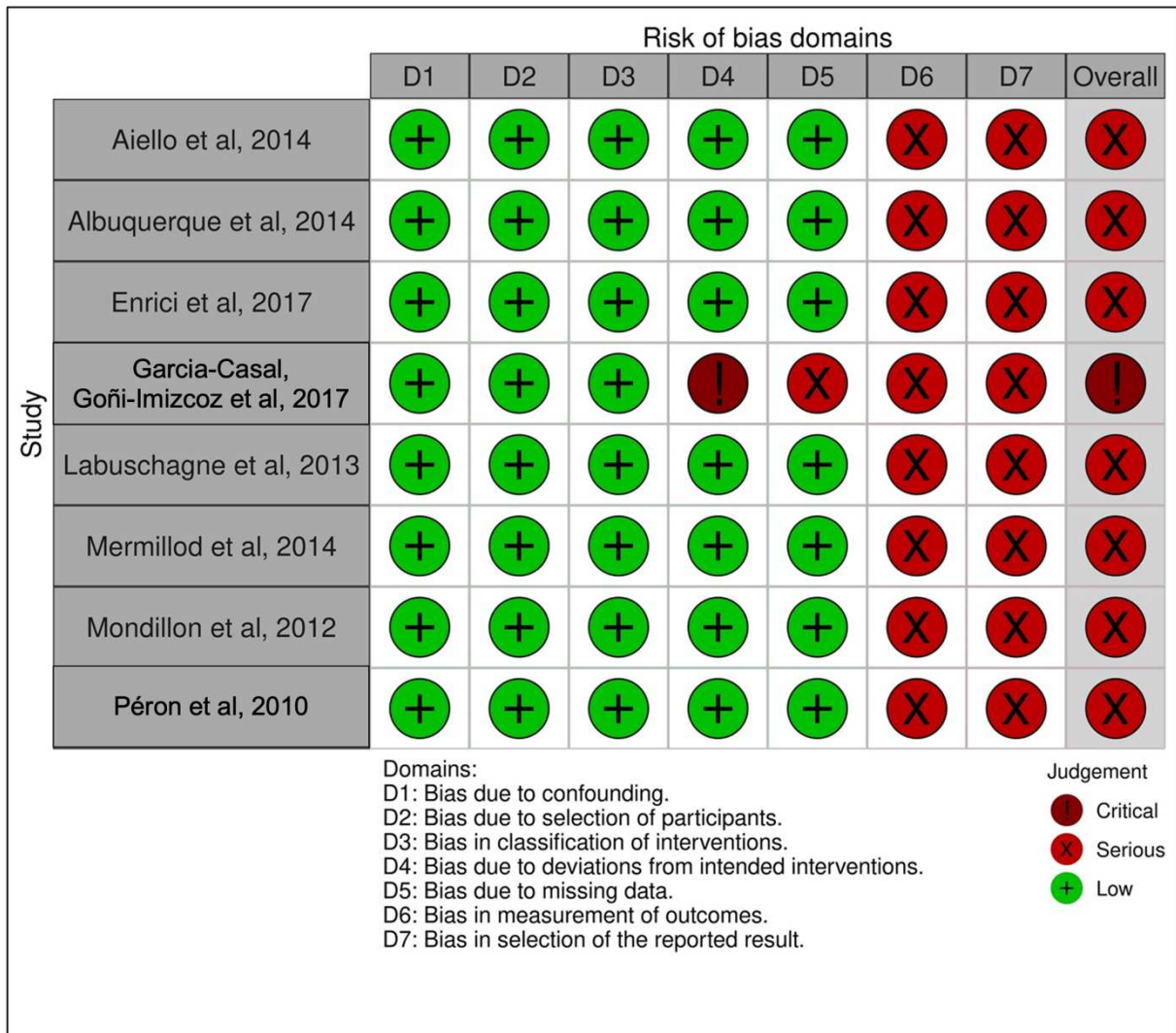


Figure 9: Traffic light plots for risk of bias assessment of non-randomized studies

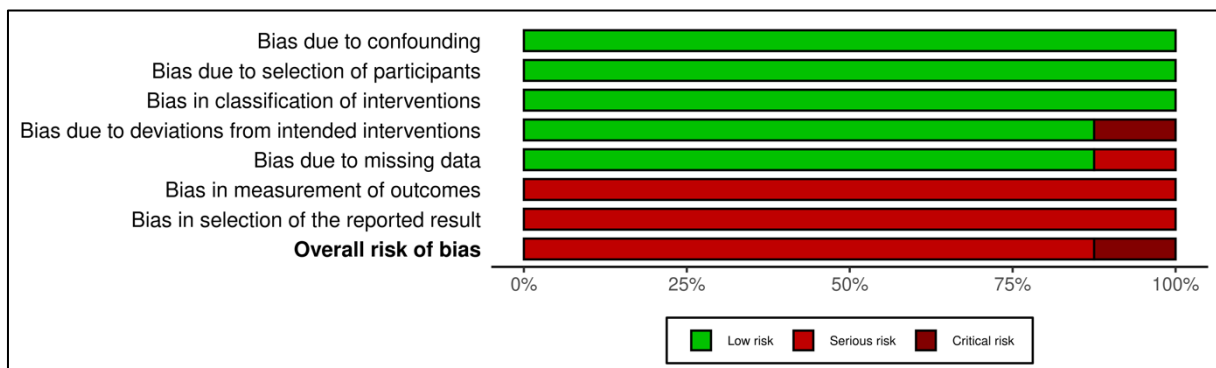


Figure 10: Plot of the percentage of risk of bias assessment at each level of risk of bias per domain for non-randomized studies

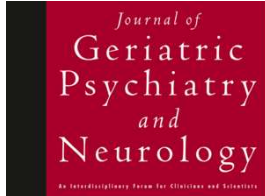
Table 3: Level of evidence by Oxford Centre for Evidence Based Medicine

	Level of evidence
Randomized studies	
Benussi et al, 2020	1B
Dan et al, 2019	1B
Jesso et al, 2011	1B
Kempnich et al, 2017	1B
McIntosh et al, 2015	1B
Polet et al, 2021	1B
Wagenbreth et al, 2019	1B
Non Randomized studies	
Albuquerque et al, 2014	2B
Aiello et al, 2014	2B
Enrici et al, 2017	2B
García-Casal, Goñi-Imizcoz et al, 2017	2B
Labuschagne et al, 2013	2B
Mermillod et al, 2014	2B
Mondillon et al, 2012	2B
Péron et al, 2010	2B

Abbreviations: 1B: individual randomized studies; 2B: individual cohort study; B: consistent level 2 or 3 studies or extrapolations from level 1 studies.



CHAPTER 6: Article 2 (EYE-TAR (AD+)): Facial emotion recognition ability can be improved in Alzheimer's disease: A randomized-controlled, single-blinded study.



This chapter is submitted in the Journal Journal of Geriatric Psychiatry and Neurology in 18/08/2023.

Facial emotion recognition ability can be improved in Alzheimer's disease: A randomized-controlled, single-blinded study.

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Submission Confirmation	
Thank you for your submission	
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Authors	MIRZAI, NAZ Galy, Edith LOUCHART DE LA CHAPELLE, Sandrine Hesse, Solange MORISOT, Adeline PESCE, Alain POLET, Kévin
Date Submitted	18-Aug-2023

ABSTRACT

Introduction

Facial emotion recognition (FER) ability is impaired in Alzheimer's Disease (AD) and associated with atypical gazing strategies when observing an expressive face. This impairment is linked to increased behavioral and psychological symptoms of dementia (BPSD) and caregiver burden.

Objective

To measure the effects of a cognitive remediation program on FER ability, eye-gaze strategies, BPSD and caregiver burden in people with AD.

Methods

A single-blinded randomized controlled study conducted in 24 AD patient-caregiver couples were assigned either to a FER cognitive remediation program (AD-TAR (Training of Affect Recognition) group: n=12) or to a cognitive stimulation program (AD-CS group: n=12). Both interventions were delivered via 2 sessions/week for 6 weeks. Outcomes were measured before and after the intervention and 1 month after intervention ended. FER ability was assessed in static and dynamic conditions with eye movements recorded by eye tracking devices. BPSD was measured using the NPI scale, as well as caregiver burden using the Zarit scale.

Results

The AD-TAR group had significantly improved FER ability, mainly for static facial expressions, also for dynamic ones. In parallel, a significant change in eye-gaze strategies for static FER and a reinforcement of observation strategies for dynamic, expressive faces were observed, with a significant decrease in BPSD and caregiver burden. These effects were maintained at 1 month.

Conclusions

We found evidence that FER remediation is effective in AD, opening new perspectives for BPSD management and quality of life improvement for AD patients and their family caregivers'.

Name of the registry: Rehabilitation of Facial Emotion Recognition in Alzheimer's Disease
URL:

<https://clinicaltrials.gov/ct2/show/NCT05267028?term=NCT05267028&draw=2&rank=1>

Registration number: NCT05267028

KEYWORDS

Alzheimer's disease, Facial emotion recognition, remediation, eye tracking, behavioral and psychological symptoms of dementia, caregiver burden

1.INTRODUCTION

Facial emotion recognition (FER) plays an important role in social cognition, providing essential information for interpersonal communication in various social contexts.¹ Basic and universal facial expressions, such as joy, fear, disgust, sadness, surprise, and anger, are recognized innately through the observation of specific emotional facial cues associated with each emotion.^{2,3}

FER ability is impaired in many neurodegenerative diseases: including multiple sclerosis,^{4,5} Parkinson's disease (PD),⁶⁻¹¹ behavioral variant of frontotemporal dementia (bvFTD),^{6,10-13} Huntington's disease,^{6,11,14,15} and Alzheimer's disease (AD).^{13,16,17} In AD, many studies concluded that FER ability is impaired for negative emotions.^{12,16,18}

FER ability engages multiple brain structures.¹⁹ Several key structures crucial for FER ability have been identified, including the amygdala,²⁰ the insula²¹ and the orbitofrontal cortex.²² These key structures are distributed within a fronto-temporal network and are

interconnected by the uncinate fasciculus.²³⁻²⁵ Other important brain structures also play critical roles in FER ability, such as the fusiform gyrus,^{20,26} and the somatosensory cortex.²⁷

FER ability tends to decline with age, particularly in the recognition of negative facial emotions, and this decline is associated with atrophy in fronto-temporal regions, especially the amygdala and insula.¹⁶ These regions are significantly impaired in bvFTD, to a lesser extent in AD, and PD.^{7,28}

FER ability impairment is observed even in the early stages of neurodegenerative diseases¹⁶ and gradually worsens in parallel with cognitive decline in AD.²⁹

Healthy participants recognize emotions faster and easier using moving faces compared to the static emotional faces traditionally used in most studies because facial movements provide important cues.³⁰ Most FER ability studies in AD have only used static facial material, and there is contradictory evidence regarding dynamic facial material. Some studies have indicated that FER ability for dynamic stimuli was preserved in early stage of AD,³¹ whereas others have suggested impairment.³² Furthermore, a study concluded that patients with dementia exhibit lower ability to recognize dynamic positive emotions such as joy and surprise, but higher ability to recognize dynamic negative emotions such as sadness and anger.³³

FER ability depends on how the emotional face is visually scanned. For example, the eyes region is critical for accurate FER ability, except when recognizing joy and disgust, where observation of the mouth region is required.³⁴⁻³⁸ Studies have highlighted that FER ability impairment is associated with modifications in eye-gaze strategies during observation of emotional faces, included decreased observation of the eyes region in psychiatric diseases such as schizophrenia or social phobia,³⁹⁻⁴⁰ neurological diseases such as multiple sclerosis,⁵ focal epilepsy,⁴¹ and neurodegenerative diseases such as AD, bvFTD and PD.^{10,42-44} This atypical gaze strategy may explain the impairment in recognizing negative emotions, which are primarily associated with the observation of the upper parts of the face.⁴⁵⁻⁴⁷

In AD, poor FER ability has been found to be associated with behavioral and psychological symptoms of dementia (BPSD),⁴⁸⁻⁴⁹ which constitutes a major factor in caregiver burden,^{32,50} especially if apathy, irritability, or disinhibition are prominent in the patient.⁵¹ Additionally, burnout and stress can impact the caregiver's own social cognition abilities by decreasing their theory of mind ability.⁵² This negative impact results in difficulties in understanding their relative's emotional and mental states, further increasing caregiver burden.⁵² Finally, a triple link is observed between impaired FER ability, atypical gaze strategy and BPSD in neurodegenerative diseases.^{10,47}

In the same line as the study by Garcia-Casal et al. ,⁵³ our preliminary study,⁴⁷ revealed that FER ability can be improved through the use of the Training of Affect Recognition program (TAR),⁵⁴ a cognitive program that aims to remediate FER ability. In our preliminary study, we assigned 4 AD patients to the TAR program and compared them to another sample of 4 matched AD patients who underwent a classical cognitive stimulation program (CS). FER ability was assessed using pictures from Ekman's Face Test,² which is a static FER ability assessment, before and after the interventions. The TAR program group exhibited significant improvements in their FER ability and demonstrated modifications in their eye gaze strategies during the observation of emotional faces, specifically an increase in the observation of the eyes region. Additionally, this group experienced a decrease in BPSD, and caregiver burden was also reduced. These beneficial effects were sustained at the 1-month post-intervention follow-up. Although the initial outcomes were promising for a novel approach to in-patient management of BPSD, further study was necessary in a larger sample and using more ecologically valid FER materials. As a result, we conducted a second study called EYE-TAR (AD+), aiming to investigate remediation of FER ability in AD and the triple interaction between FER impairment, atypical gaze strategy, and BPSD in a larger population.

2.METHODS

Standard protocol approvals, registrations, and patient consents

The study protocol received approval from the Princess Grace Hospital Steering Committee for Clinical Research (Monaco) and was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and its later amendments. Each participant received a detailed description of the study modalities and signed informed consent. This trial, recorded as EYE-TAR(AD+), has been registered at ClinicalTrials.gov: NCT05267028.

Study Population

From February 2022 to January 2023, a total of 17 patients with AD and their family (referred to as caregiver-patient couples) were recruited at the Memory Center of the Rainier III Clinical Gerontology Center of the Princess Grace Hospital of Monaco. The recruitment was conducted by physicians specializing in geriatrics or psychiatry as part of routine care.

Inclusion criteria for the patients with AD were as follows: (1) male or female fulfilling the International Working Group-2 diagnostic criteria for AD⁵⁵; (2) Mini-Mental State (MMS-E)⁵⁶ ≥ 15 ; (3) accompanied by a family caregiver and whose participation in a CS program was recommended in Memory Center of the RAINIER III Center (Princess Grace Hospital - Monaco); (4) written informed consent signed by both the patient and the family caregiver. Regarding the patient, the following exclusion criteria were applied: (1) general anesthesia within 3 months; (2) history of psychiatric and/or neurological disorder (other than the diagnosed neurodegenerative pathology); (3) history of alcoholism or drug addiction; (4) ophthalmological or neurological problems preventing a video-oculography examination; (5) oculomotor disorders such as "fixation disorders" or "smooth pursuit disorders"; (6) neurovisual disorders (visual agnosia, prosopagnosia, visuospatial disorder or visuoperceptual disorder) or aphasia.

To increase the sample size, the outcomes of the 8 caregiver-patients couples who participated in the preliminary study⁴⁷ were also included in the current study. These participants were recruited from March 2019 to January 2020. The location and the reglementary approval procedure were the same, and the inclusion and exclusion criteria were identical. The study design was also similar, involving the same interventions and evaluations under the same conditions at each time point, except for the dynamic FER assessments which was not performed in this preliminary study.

Thus, our sample sized expanded to include a total of 25 caregiver-patient couples with AD.

Study Design

This study was a randomized controlled trial with a single-blind design. The participant couples recruited to the study were randomly assigned to one of two groups: the AD-TAR experimental group, which received the TAR rehabilitation program intervention, and the AD-CS control group, which received the classical CS program intervention. The randomization was based on the patients' consultation dates at the Memory Center during the study year. The allocation was done in chronological order by the investigators, with the first four couples assigned to the experimental group and the subsequent four couples assigned to the control group, and so on, maintaining a 1:1 ratio.

A blinding method was implemented as follows: (1) Participants and outcome assessors were blinded to the type of intervention, ensuring that they were unaware of whether the participant received the TAR rehabilitation program or the classical CS program. (2) The individuals responsible for delivering the interventions were aware of the assigned interventions given to the patients. Both the TAR and CS interventions consisted of 1-hour sessions conducted in groups of 4 to 5 participants, taking place twice a week for 6 weeks. Assessments were conducted at three-time points: baseline (T0) before the start of the intervention, at the

end of the intervention (T1), and at a 1-month post-intervention (T2). During these assessments, each patient underwent clinical evaluations and an eye-tracking procedure. Additionally, caregivers participated in interviews with a neuropsychologist to evaluate the BPSD in their loved ones and assess caregiver burden. The study design is illustrated in Figure 1.

Our completed CONSORT checklist based on CONSORT reporting guidelines⁵⁷ is presented in Supplementary Material 1.

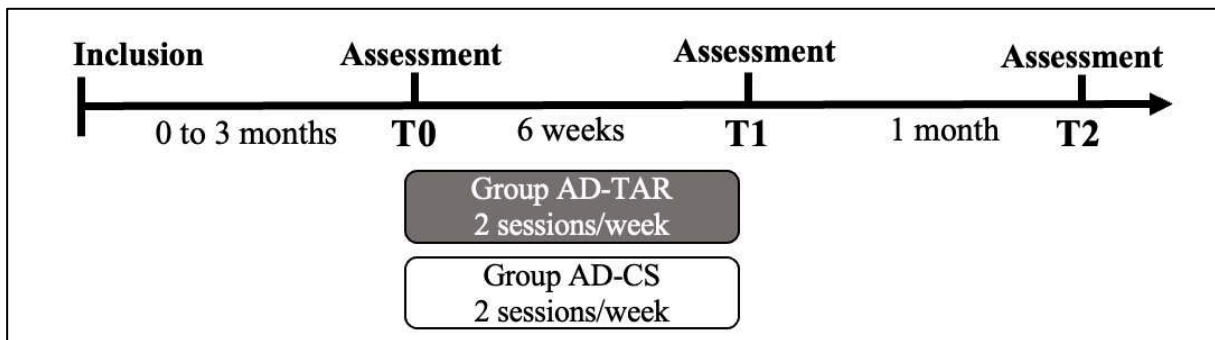


Figure 1: Study design. AD, Alzheimer’s Disease; TAR, Training of Affect Recognition; CS, Cognitive Stimulation.

Training of Affect Recognition (TAR)

TAR⁵⁴ is a FER ability targeted cognitive remediation program that consists of three modules, each consisting of four sessions, for a total of 12 sessions. Each session lasts one hour, and two sessions were conducted every week during six weeks. The first module aimed to train the identification and discrimination of the prototypical facial signals of the six primary emotions. The second module promoted the holistic processing of emotional faces and faster recognition and distinction of low-intensity expressions. The third module addressed the recognition of emotions in social situations and ambiguous emotions. The sessions were both paper-and-pencil and computer-based.

Cognitive Stimulation

Patients assigned in AD-CS group had a total of 12 sessions of a CS program used in routine care in Rainier III memory center. Each session lasts one hour, and two sessions were conducted every week during six weeks according to the current practice of our memory center.

Each session began with a review of current events (memorization and recall at the end of the session), followed by a reminiscence exercise (recall of autobiographical events). The session ended with two or three exercises (paper-and-paper or computerized), targeting each cognitive function to be stimulated (episodic, semantic, or working memory, language, attention, executive functions, praxis, visual gnosis, and visuo-spatial functions).

Assessments

Global Cognitive Function

Assessed by the MMS-E.⁵⁶

Facial Emotion Recognition

Static FER

Static FER ability was assessed using 28 photographs taken from Ekman's faces set,² including 4 photos for each basic emotion (joy, anger, fear, surprise, disgust, sadness, and neutral), resulting in a total score out of 28. The photos were in black and white, with a format of 22.2 x 14.7 cm.

Dynamic FER

Dynamic FER ability was assessed using 28 videos from the Amsterdam Dynamic Facial Expression Set (ADFES).⁵⁸ Each video represented one of the four basic emotions, resulting in a total score of 28. The videos featured actors expressing emotions in front of the camera and were in color. The format of the videos was similar to the photos from Ekman's faces, and each video started with a neutral face and gradually intensified to reach the peak intensity of the emotion. Assessing dynamic emotions allows for a more ecological and realistic evaluation of the primary emotions.

In both the static and dynamic conditions, each photo or video was presented on a screen with specific specifications. The screen had a size of 22 inches and a resolution of 1920x1080 pixels, with a refresh rate of 60 Hz. The screen's luminance was set to 250 cd/m², and the static

contrast ratio was 1000:1. The maximum display time for each photo or video was 8 seconds (Figure 2).

During the task, participants were instructed to fixate on a central point on the screen between each photo or video presentation. When a new photo or video appeared, the participant had to focus on it. The task for the participant was to recognize and identify the emotion being expressed among the seven options displayed on the screen. The options included the six primary emotions (joy, anger, fear, surprise, disgust, sadness) as well as a choice for "neutral." Participants were required to provide their responses orally.

Eye-tracking Procedure

Eye-gaze strategies were studied using two eye tracking devices. A Mobile EyeBrainT2® (SURICOG) to measure eye movements during static FER. It is a free head-mounted eye-tracker (helmet) equipped with two infrared cameras recording eye movements at a frequency of 300 Hz (accuracy 0.25° at 60 cm from the screen). And a Tobii X3 120 Eye Tracker to measure eye movements during dynamic FER. This is a static eye-tracker fixed on a screen, placed 60 cm away from the subject, using infrared cameras to record eye movements at a frequency of 120 HZ (accuracy 0.24°).

Both devices underwent an initial calibration process involving fixation on consecutive points to ensure accurate measurements. During the experiment, the devices recorded various metrics for each observed photo or video. These metrics included the number of fixations, the duration of each fixation, and the exploration times (measured in milliseconds) for four specific regions of interest: the entire face, the eyes, the nose, and the mouth (as shown in Figure 2).

In the analysis, a fixation was defined as the eyes remaining in a 1°x1° zone for at least 100 milliseconds, as established by Manor and Gordon.⁵⁹

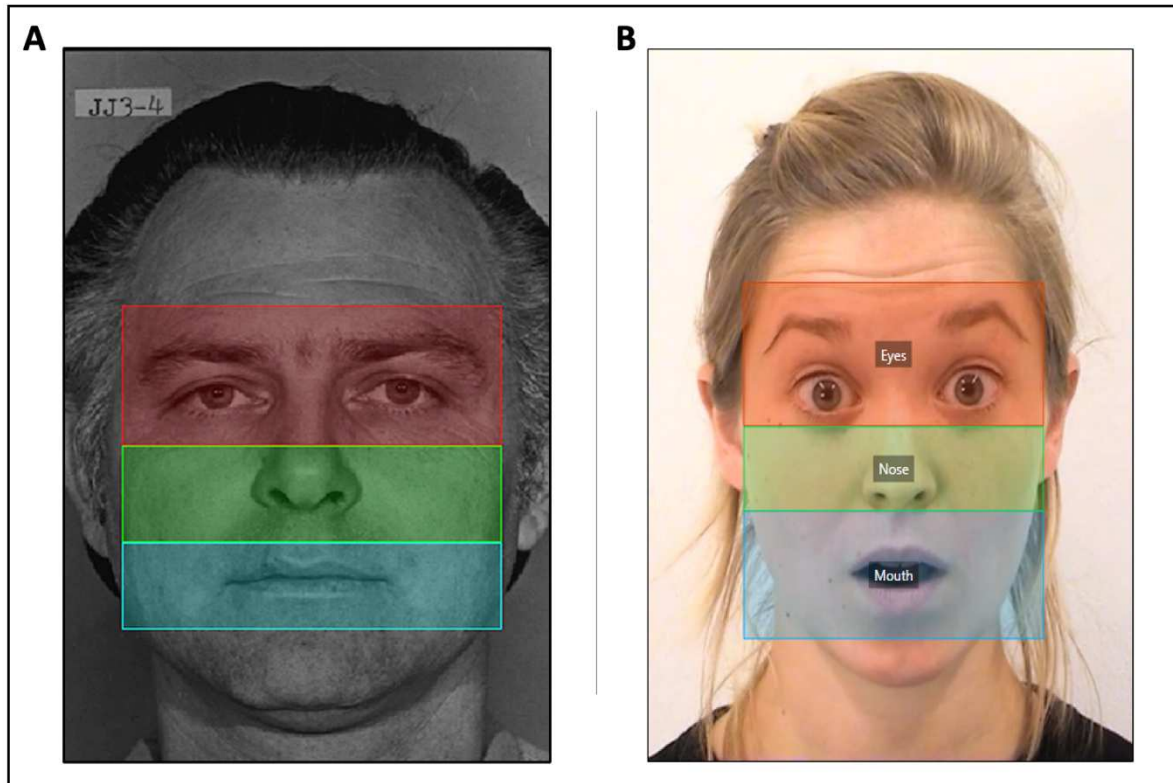


Figure 2. Examples of faces used for FER assessments. **A.** Neutral face from Ekman’s Faces Test for static FER and **B.** Surprised face (at 100% intensity) from ADFES for dynamic FER, with the representation of the three ROI for analysis: the eyes region in red, the nose region in green and the mouth region in blue. Images were used with the permission of the Paul Ekman Group and Van der Schalk et al., 2011.

Behavioral and Psychological Symptoms of Dementia

To screen the BPSD, the Neuropsychiatric Inventory (NPI)⁶⁰ was used. NPI consists of ten behavioral items (delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, and aberrant motor behaviors), and two neurovegetative symptoms (sleep and appetite disorders). A neuropsychologist conducted the NPI assessment during an interview with the primary family caregiver of the patient. For each BPSD item, a score was obtained by multiplying the frequency (rated on a scale of 1 to 4) and the severity (rated on a scale of 1 to 3). The maximum score for each item is thus 152(5 4 x 3). The total score on the NPI ranges from 0 to 144, encompassing all the assessed behavioral and neurovegetative symptoms.

Caregiver's Burden

The burden experienced by the primary family caregiver was assessed using the Zarit scale⁶¹. The scale consists of 22 questions that evaluate the caregiver's perception of the physical, emotional, and financial burdens associated with providing care. Each question is rated of 0 to 4, and the total score of the scale ranges from 0 to 88. A higher score indicates a greater burden experienced by the caregiver.

Outcome measures

The primary endpoint was FER performances (in static or dynamic condition), defined as the change from baseline and comparison of FER scores and responses time between AD-TAR group and AD-CS group. The secondary endpoints were defined as the change from the baseline and comparison between AD-TAR group and AD-CS group of (1) eye-gaze strategies during static and dynamic FER (number and duration of fixations on regions of interest, timeline of eye fixations), (2) BPSD (NPI items), (3) caregiver burden (Zarit score), and (4) global cognitive performance (MMSE score).

Statistical analyses

In the absence of available data from previous research, we were not able to estimate the sample size needed. However, based on the feasibility considerations at our clinic, we have estimated a total sample size of 20 patient-caregiver couples, with 10 patients allocated to the AD-TAR group and 10 patients allocated to the AD-CS group.

The characteristics of the participants were reported using either mean and standard deviation (for continuous variables) or sample size and percentages (for categorical variables), depending on their nature. A comparison between the AD-TAR and AD-CS groups was conducted using non-parametric tests, specifically the Fisher test for categorical variables and the Wilcoxon test for continuous variables. Comparisons between assessments were also made using the paired Wilcoxon test. Statistical significance was determined using a threshold of $P <$

0.05, indicating that results with a p-value below this threshold were considered statistically significant. All statistical analysis were performed using R version 3.6.2 software.

Data availability

The dataset generated and analyzed during the current study is available from the corresponding author upon reasonable request.

3.RESULTS

Sample Characteristics

A total of 25 caregiver-patient couples were initially enrolled and randomized. One couple dropped out from the AD-TAR group during the second TAR session because they did not desire to continue the program. Therefore, data from 24 caregiver-patient couples were analyzed, but due to the COVID-19 lockdown, MMS-E and FER ability outcomes were missing for 4 participants in the AD-CS group. Furthermore, the 8 caregiver-patient couples from the preliminary study did not undergo dynamic FER ability assessment (see detail in *Methods, Study population*).

The sociodemographic and clinical characteristics of the 24 caregiver-patient couples are reported in Table 1.

During the study, it was found that 6 out of 12 patients in the AD-TAR group were receiving anticholinesterase treatment, while 4 out of 12 patients in the AD-CS group were on the same treatment.

The participation rate in the programs' sessions was comparable between groups (AD-TAR: $M = 97.2\%$, $SD = 7.4$, AD-CS: $M = 98.6\%$, $SD = 4.9$, $P > .05$). Furthermore, no unintended effects were observed in either of the groups.

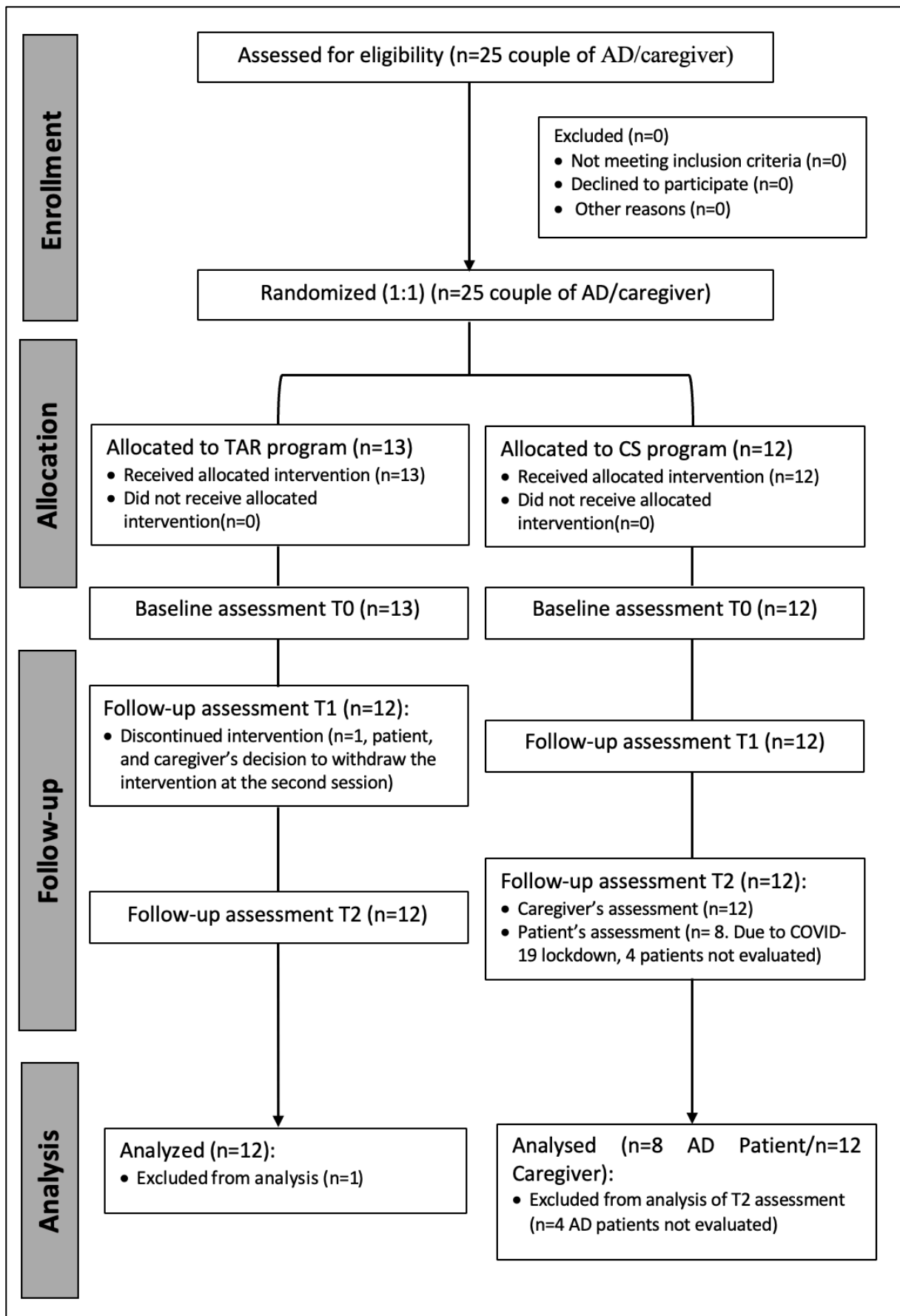


Figure 3: CONSORT 2010 Flow Diagram. AD, Alzheimer's Disease

Table 1: Sociodemographic and Clinical Characteristics of each participant

	Age	Sex (female/male)	Years of Education	MMS-E	Nature of Caregiver
Participants Group AD-TAR (sd)	75.25 (8.88)	6f/6m	11.25 (3.93)	20.75 (3.22)	
N°1	74	f	17	19	Spouse
N°2	83	m	12	20	Spouse
N°3	75	f	9	23	Daughter
N°4	81	m	6	21	Spouse
N°5	64	f	17	18	Son
N°6	56	m	11	19	Spouse
N°7	70	f	9	18	Daughter
N°8	88	m	15	24	Daughter
N°9	78	f	9	28	Spouse
N°10	80	m	14	21	Spouse
N°11	82	m	11	22	Daughter
N°12	72	f	5	16	Daughter
Participants Group AD-CS (sd)	75.25 (6.76)	7f/5m	12.08 (3.12)	20.08 (2.94)	
N°13	80	m	15	22	Spouse
N°14	78	f	12	27	Spouse
N°15	73	f	15	19	Spouse
N°16	83	f	12	17	Daughter
N°17	67	f	15	17	Spouse
N°18	86	f	5	17	Spouse
N°19	78	m	9	21	Spouse
N°20	73	f	12	22	Daughter
N°21	63	m	12	19	Spouse
N° 22	76	m	15	20	Spouse
N° 23	68	f	9	22	Spouse
N° 24	78	m	14	18	Daughter

Abbreviations: AD, Alzheimer's Disease; CS, cognitive stimulation; SD, standard deviation; TAR, Training of Affect Recognition

Baseline results

Clinical and demographic characteristics

Table 2 indicates that the 2 groups were similar in terms of age, sex, education and level of cognitive impairment (MMS-E scores) matched (all $P > .05$).

Table 2: Comparisons of sociodemographic and clinical characteristics of each group

Mean (sd)	AD-TAR	AD-CS	t	P
N	12	12		
Age	75.2 (8.9)	75.2 (6.8)	0	1
Sex (female/male)	6/6	7/5	Fisher	1
Education (years)	11.2 (3.9)	12.1 (3.1)	0.6	.57
MMS-E	20.8 (3.2)	20.1 (2.9)	0.5	.60

Variables were compared between each group using the Student test.

Abbreviations: AD, Alzheimer's Disease; CS, cognitive stimulation; TAR, Training of Affect Recognition.

Comparison of difficulty between static and dynamic facial emotion recognition test

To compare the difficulty level between the static and dynamic FER assessment, we have pooled participants who completed both Ekman's Faces test and ADFES (n=16) at baseline. The results revealed a significantly higher total score for the ADFES assessment than the Ekman's Faces test (ADFES: M = 20.8, SD = 4.9; Ekman's Faces test: M = 17.8, SD = 4.8, $p = 0.01$). Moreover, performances were significantly higher in recognising fear, sadness, and disgust (all $p < 0.05$ for all variables). Detailed results can be found in Table 3.

Table 3: Comparison of difficulty between static and dynamic facial emotion recognition test

Mean (sd)	Ekman's Faces Test	ADFES	V	P
N	16	16		
Total Score	17.8 (4.8)	20.8 (4.9)	94	.01*
Score Joy	3.8 (0.8)	3.5 (0.8)	3	.20
Score Fear	1.6 (1.2)	2.6 (1.5)	49	.03*
Score Anger	2.6 (1.3)	2.4 (1.5)	42	.49
Score Sadness	1.3 (1.1)	2.4 (1)	95	.006*
Score Disgust	2.6 (1.2)	3.3 (1)	57	.03*
Score Surprise	2.9 (1.3)	3.7 (0.6)	44	.10
Score Neutral	3.1 (1.1)	2.9 (1.3)	15	.39

The performances of the 8 participants in each group for whom static and dynamic FER data could be collected during the T0 evaluation were pooled for the static FER (Ekman's Faces Test) and for the dynamic FER (ADFES), then compared using the Wilcoxon test, to compare the difficulty between these tests. * Significant at $p < .05$.

Abbreviations: AD, Alzheimer's Disease; CS, cognitive stimulation; TAR, Training of Affect Recognition; SD, standard deviation; V, Wilcoxon test.

FER performances

FER performances of each group are detailed in Table 4 and illustrated in Figure 4.

Performances for static FER

At baseline, there were no significant differences observed between the groups in terms of FER scores, both in the global score (as depicted in Figure 4) and in the recognition of each specific emotion ($P > .05$ for all comparisons). Regarding the response time, the AD-CS group exhibited overall significantly slower response times compared to the AD-TAR group (AD-TAR: M = 4.4s, SD = 1.1, AD-CS: M = 5.2s, SD = 0.7, $P = .03$). Specifically, significant differences were observed in the recognition of joy and disgust, (all, $P < 0.05$).

Performances for dynamic FER

No significant differences were found between the groups in terms of FER scores or response times in the ADFES test (all $P > .05$).

Eye tracking Analysis

Table 5 presents eye-tracking data indicating significant differences in eye gaze behaviors during FER between the groups.

Gaze strategies during static FER

Globally no significant differences in gaze strategies for recognizing static emotions were found between the groups (all $P > .05$). However, two subtle differences were highlighted: the AD-CS group exhibited significantly more fixations on the nose when recognizing the joy and more fixations on the face when recognizing disgust (all $P < .05$). No significant differences in gaze strategies were observed for other emotions (all $P > .05$).

Gaze strategies during dynamic FER

Globally, no significant differences in gaze strategies for recognizing dynamic emotions were found between the groups (all $P > .05$). The only significant difference observed was that the AD-CS group had more fixations in the mouth region during joy recognition compared to the AD-TAR group (AD-TAR: $M = 1$, $SD = 0.9$, AD-CS: $M = 2.2$, $SD = 1.2$, $P = .04$).

BPSD and Caregiver Burden

At baseline, no significant differences were observed between the groups in terms of BPSD and caregiver burden, as indicated by the total score and sub-scores in the NPI (Table 4 and Figure 4) (all $P > .05$) and the Zarit scale (AD-TAR: $M = 26.6$, $SD = 12.8$, AD-CS: $M = 22.4$, $SD = 12.3$, $P = .45$).

Post-intervention assessments (T1 and T2): performances comparisons between groups

Comparisons between the groups are presented in Table 4 and Figure 4.

Global cognition

MMS-E performances remained similar between groups at T1 and T2.

FER performances

Performance for static FER

At T1, the AD-TAR group achieved significantly higher total scores on the Ekman's Face test than the AD-CS group. (AD-TAR: $M = 21.3$, $SD = 3.1$, AD-CS: $M = 17.5$, $SD = 4.2$, $P = .02$). This difference was not observed at T2 (AD-TAR: $M = 20.4$, $SD = 5$, AD-CS: $M = 18.8$, $SD = 4.3$, $P = .30$). In particular, the AD-TAR group obtained significantly higher scores for sadness and neutral recognition at T1 (all $P < .05$). These significant differences were not observed at T2 (all $P > .05$). Conversely, at T1, the AD-TAR group exhibited a significantly lower score for surprise recognition compared to the AD-CS group at T1 (AD-TAR: $M = 2.4$, $SD = 1.2$, AD-CS: $M = 3.4$, $SD = 0.7$, $P = .02$). However, this significant difference was not observed at T2 (AD-TAR: $M = 3.3$, $SD = 0.9$, AD-CS: $M = 3.2$, $SD = 0.7$, $P = .71$).

Regarding response time, the AD-TAR group consistently exhibited faster response times compared to the AD-CS group at each assessment (T0, T1, T2) (Mean response time, all $P < .05$). Specifically, at T1, the AD-TAR group showed faster response times than the AD-CS group for fear, sadness, and neutral recognition, and these differences sustained at T2 for sadness and neutral recognition.

Lastly, in contrast to the baseline, there was no longer a significant difference between the groups in terms of response times for joy recognition (T0: AD-TAR: $M = 3.1s$, $SD = 1.5$, AD-CS: $M = 4.4s$, $SD = 1$, $P = .02$; T1: AD-TAR: $M = 3.8s$, $SD = 1.7$, AD-CS: $M = 4.1s$, $SD = 1.3$, $P = .62$; T2: AD-TAR: $M = 3.2s$, $SD = 2.1$, AD-CS: $M = 3.6s$, $SD = 0.9$, $P = .06$).

All other comparisons in recognition scores and response times between the groups were not significant at both T1 and at T2 (all $P > .05$).

Performances for dynamic FER

No differences in ADFES scores were observed between the groups for total score at both T1 and T2 (all $P > .05$). The AD-TAR group was faster to respond at T2 compared to the AD-CS group ($P < .05$). The only significant difference between the groups is that the AD-TAR group exhibited faster recognition of sadness compared to the AD-CS group at the T2 assessment. (AD-TAR: $M = 5.2s$, $SD = 0.9$, AD-CS: $M = 6.3s$, $SD = 0.6$, $P < .05$).

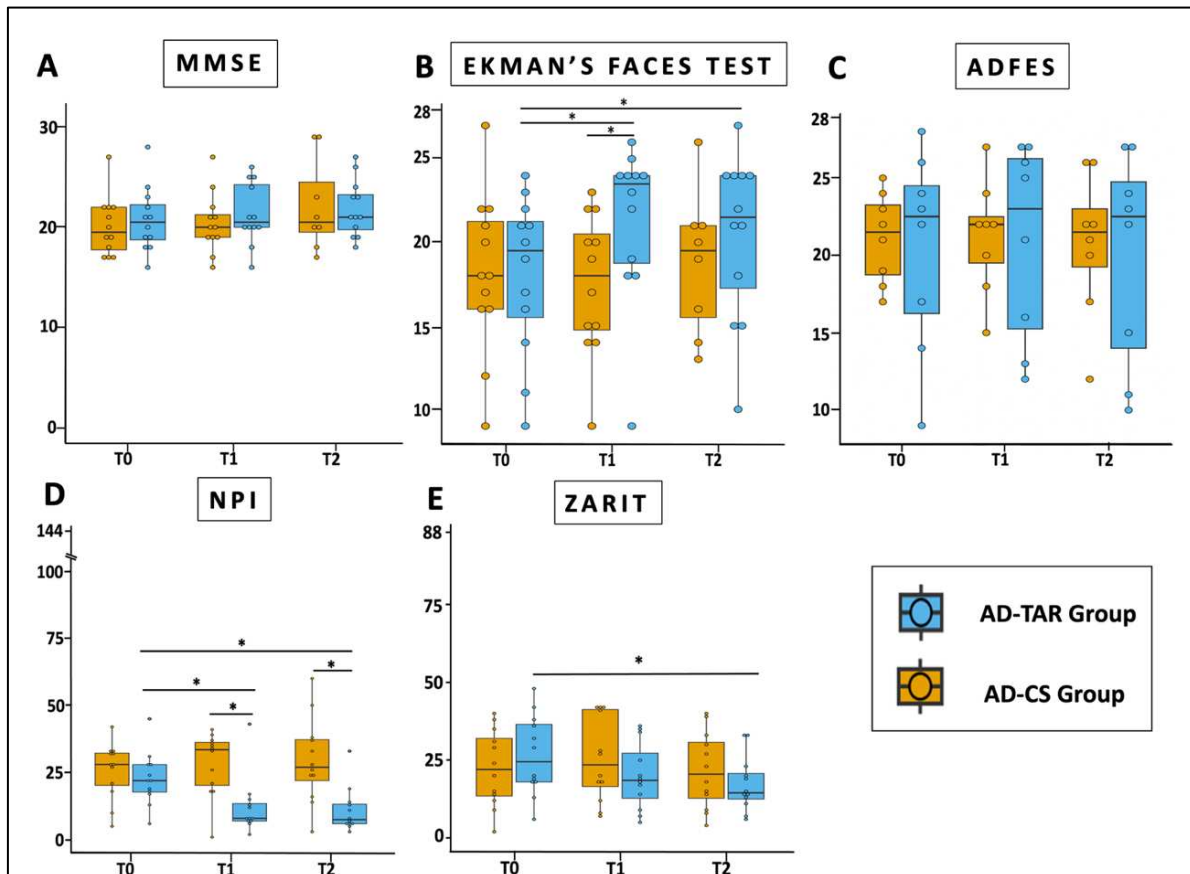


Figure 4. Evolution of clinical and FER assessments. **A.** Evolution of global cognition performances; **B.** Evolution of static FER performances; **C.** Evolution of dynamic FER performances; **D.** Evolution of BPSD; **E.** Evolution of family caregiver burden level in each group. AD, Alzheimer's Disease; TAR, Training of Affect Recognition; CS, Cognitive Stimulation. *Significant at $P < .05$.

Table 4: Comparisons of global cognition, facial emotion recognition performances, level of behavioral and psychological symptoms of dementia and level of caregiver burden at each assessment between groups.

Mean (sd)	T0 assessments				T1 assessments				T2 assessments			
	AD-TAR	AD-CS	W	P	AD-TAR	AD-CS	W	P	AD-TAR	AD-CS	W	P
MMSE												
N	12	12			12	12			12	8		
Score	20.8 (3.2)	20.1 (2.9)	62	.58	21.3 (3.1)	20.4 (3)	58	.43	21.8 (2.8)	22.1 (4.6)	45	.85
Ekman's Faces Test												
N	12	12			12	12			12	8		
Total Score	18.1 (4.8)	18.2 (4.8)	70	.91	21.3 (4.7)	17.5 (4.2)	32	.02*	20.4 (5)	18.8 (4.3)	34	.30
Mean Response Time	4.4s (1.1)	5.2s (0.7)	110	.03*	3.9s (1.4)	5.3s (0.9)	117	.01*	3.7s (1.4)	4.7s (0.9)	76	.03*
Score Joy	3.7 (0.9)	3.9 (0.3)	79	.55	3.8 (0.6)	3.8 (0.6)	67	.62	3.8 (0.6)	3.9 (0.4)	51	.80
Response time Joy	3.1s (1.5)	4.4s (1)	114	.02*	3.8s (1.7)	4.1s (1.3)	81	.62	3.2s (2.1)	3.6s (0.9)	73	.06
Score Fear	1.5 (1.2)	1.7 (1.3)	78	.74	2 (1.3)	1.4 (0.9)	52	.24	1.4 (1.2)	1.8 (1.5)	54	.66
Response time Fear	4.2s (1.4)	4.2s (0.9)	65	.71	3.8s (1.7)	5s (1.1)	110	.03*	3.5s (1.4)	4s (1.3)	63	.26
Score Anger	2.8 (1.3)	2.7 (1.4)	67	.79	3 (1.1)	2.5 (1.4)	57	.38	2.8 (1.1)	2.5 (1.4)	42	.66
Response time Anger	4.3s (1.4)	5.6s (1.5)	106	.05	4.6s (1.3)	5.8s (1.4)	106	.05	4.2s (1.5)	5.5s (1.5)	71	.09
Score Sadness	1.2 (1.1)	1.4 (1)	78	.74	3.3 (1.2)	1.4 (1)	17	.001*	2.6 (1.4)	1.9 (1)	34	.27
Response time Sadness	6s (1.1)	6.1s (1.2)	79	.71	4s (1.6)	6.1s (1)	125	.002*	4.1s (1.7)	6.1s (0.9)	80	.02*
Score Disgust	2.8 (1.3)	2.8 (1.1)	70	.92	3.1 (1.4)	2.4 (1.2)	46	.12	3.2 (1.1)	3 (0.9)	42	.65
Response time Disgust	4.5s (1.3)	6s (1.2)	119	.008*	3.7s (1.7)	5.4s (1.5)	114	.02*	3.6s (1.7)	4.3s (1.7)	62	.30
Score Surprise	2.9 (1.4)	2.8 (1.1)	65	.69	2.4 (1.2)	3.4 (0.7)	110	.02*	3.3 (0.9)	3.2 (0.7)	43	.71
Response time Surprise	4.2s (1.1)	4.7s (1.4)	88	.37	3.8s (1.7)	4.8s (1.4)	99	.13	3.5s (1.9)	3.9s (1.1)	65	.22
Score Neutral	3.2 (0.7)	2.9 (1.2)	67	.78	3.7 (0.7)	2.6 (1.3)	36	.02*	3.3 (1.1)	2.5 (1.4)	31	.16
Response time Neutral	4.7s (1.8)	5.7s (1.2)	101	.11	3.4s (2)	5.6s (1.4)	111	.03*	3.5s (1.7)	5.2s (1.8)	75	.04*
ADFES												
N	8	8			8	8			8	8		
Total Score	20.4 (6.5)	21.1 (2.9)	31	.96	20.9 (6.4)	21.2 (3.7)	31	.96	19.9 (6.9)	20.8 (4.6)	30	.87
Mean Response Time	5.1s (1.1)	5.3s (1.1)	39	.53	5s (1)	5s (1.1)	30	.88	4.7s (1)	5.7s (0.8)	52	.05*
Score Joy	3.5 (0.9)	3.5 (0.8)	30	.85	3.6 (1.1)	4 (0)	36	.38	3.5 (1.1)	4 (0)	40	.17
Response time Joy	4.5s (1.4)	4.4s (1.4)	31	.96	4s (0.7)	3.8s (0.8)	32	1	4.3s (1.5)	5s (1)	45	.21
Score Fear	2.2 (1.9)	3 (0.8)	36	.70	2.2 (1.4)	3.1 (0.8)	45	.19	2.4 (1.7)	2.4 (1.8)	33	.96
Response time Fear	4.6s (1)	5s (1.4)	42	.34	4.7s (1.3)	4.6s (1.2)	31	.96	4.2s (1.1)	5.2s (1.3)	47	.13
Score Anger	2.2 (1.9)	2.5 (1.1)	32	1	2.5 (1.3)	3.2 (1.2)	44	.2	2.5 (1.3)	2.5 (1.3)	32	1
Response time Anger	5.7s (1.1)	6.3s (1.4)	42	0.34	6.2s (1.4)	5.6s (1.3)	23	.37	5.5s (1.5)	6.4s (1)	43	.27
Score Sadness	2.4 (1.3)	2.4 (0.7)	32	1	2.8 (1.3)	2.1 (1.1)	23	.33	2.2 (1.4)	1.9 (1)	27	.62
Response time Sadness	5.8s (1.5)	5.8s (1.3)	33	1	5.7s (1.2)	6s (1.2)	36	.71	5.2s (0.9)	6.3s (0.6)	53	.03*
Score Disgust	3.4 (0.7)	3.2 (1.2)	33	.95	2.9 (1.4)	2.9 (0.8)	30	.87	3.1 (1.2)	3.4 (0.7)	33	.95
Response time Disgust	4.4s (1.2)	5.1s (2)	38	.56	5s (2.1)	4.7s (2)	32	1	4.1s (1.4)	5.6s (1.4)	50	.07
Score Surprise	3.8 (0.5)	3.6 (0.7)	31	.95	3.4 (0.9)	3.5 (0.5)	32	1	3.2 (0.9)	3.6 (0.5)	39	.44
Response time Surprise	4.2s (1)	4.2s (1.4)	28	.67	3.9s (1.2)	4.1s (1.4)	36	.71	4.1s (1.2)	5.1s (1.1)	47	.14
Score Neutral	2.9 (1.6)	2.9 (1)	30	.82	3.5 (1.1)	2.4 (1.3)	16	.07	2.9 (1.6)	3 (1.2)	33	1
Response time Neutral	6.3s (1.4)	6.4s (0.8)	33	.96	5.6s (1.3)	6s (1.1)	39	.49	5.2s (1.6)	6.2s (1.8)	41	.37
NPI												
N	12	12			12	12			12	12		
Total Score	22.8 (9.8)	25.8 (10.5)	91	.30	12.2 (10.6)	28.2 (11.8)	121	.005*	10.9 (8.3)	29.4 (15.6)	124	.003*
Delusions	0.6 (1)	1.9 (2.8)	85	.41	0.6 (1.2)	2.2 (2.7)	100	.08	0.3 (0.7)	0.7 (1.4)	75	.88
Hallucinations	0 (0)	0.5 (1.7)	78	.36	0 (0)	0.5 (1.7)	78	.36	0 (0)	0.3 (1.2)	78	.36
Agitation/Aggression	0.8 (1.8)	1.7 (1.9)	101	.07	0 (0)	1.7 (2.4)	102	.02*	0.3 (0.7)	1.5 (2)	99	.09
Dysphoria/Depression	2.8 (3.5)	2.8 (2.4)	79	.72	1 (1.8)	2.9 (2.7)	108	.03*	1.1 (2)	2.3 (3.1)	88	.33
Anxiety	4.8 (3.5)	5.7 (3.1)	84	.52	2.8 (1.9)	5.3 (2.6)	109	.03*	2.1 (2.5)	5.6 (2.9)	120	.006*
Euphoria/Elation	0.2 (0.5)	0.2 (0.6)	62	.37	0.3 (1.2)	0.3 (0.8)	77	.65	0.5 (1.2)	0 (0)	60	.17
Apathy/Indifference	7 (2.5)	5.9 (3.3)	55	.27	2.7 (2.3)	5.2 (3.2)	103	.07	2.2 (2.2)	6 (4.1)	113	.02*
Disinhibition	0.8 (1.1)	0.3 (0.7)	62	.47	0.5 (1.2)	0.8 (1.2)	87	.30	0.4 (1)	0.8 (1.3)	88	.26
Irritability/Lability	1.3 (1.4)	1.7 (2)	73	1	1.2 (1.5)	1.8 (1.9)	85	.45	0.4 (0.7)	3.6 (3.6)	119	.005*
Aberrant motor	1.9 (2.6)	1.7 (1.8)	70	.93	0.8 (1.4)	2 (2.7)	90	.24	1.2 (1.9)	3.3 (3.7)	99	.10
Nighttime behavior	0.9 (2.4)	1.2 (1.7)	88	.26	1.3 (2)	1.8 (2.5)	80	.66	0.8 (1.9)	2 (3.2)	82	.49
Appetite/Eating	1.6 (2.4)	2.3 (3.9)	74	.95	1.1 (1.7)	3.8 (2.6)	116	.009*	1.4 (1.4)	3.2 (2.7)	104	.07
ZARIT												
N	12	12			12	12			12	12		
Score	26.6 (12.8)	22.4 (12.3)	59	.45	19.9 (10.7)	25.4 (13.6)	91	.28	17.3 (8.8)	21.7 (12.2)	87	.40

Variables were compared between each group using the Wilcoxon test. * Significant at $p < .05$. Abbreviations: AD, Alzheimer's Disease; CS, cognitive stimulation; NPI, Neuropsychiatric Inventory; TAR, Training of Affect Recognition; SD, standard deviation; W, Wilcoxon test.

Eye tracking Analysis

Significant differences in eye gaze behaviors during FER at each assessment between the groups are shown in table 5.

Gaze strategies during static FER

Globally, the average fixation duration on the face during FER became significantly longer at T1 and T2 for the AD-TAR group compared to the AD-CS group (all $P < .05$). Especially, the AD-TAR group exhibited longer average fixation durations on the total face for disgust at the T2 assessment. Additionally, this difference in average fixation durations was also observed on the eyes region for anger and surprise at both T1 and T2 assessments, for fear only at the T1 assessment, for the neutral condition only at T2 assessment and on the nose region for joy recognition at T1 assessment (all $P < .05$).

Regarding the number of fixations, the AD-CS group exhibited significantly more fixations on the face for disgust recognition than the AD-TAR group at the T0 assessment (AD-TAR: $M = 6$, $SD = 1.4$, AD-CS: $M = 9.5$, $SD = 3.1$, $P = .008$). However, this difference was no longer observed post-intervention at T1 and T2 assessments (all $P > .05$).

We also observed a significant difference on the nose region for joy recognition: the AD-CS group made significantly more fixations than the AD-TAR group at the T0 assessment (AD-TAR: $M = 1$, $SD = 0.5$, AD-CS: $M = 1.9$, $SD = 1.6$, $P = .04$). However, this difference was reversed post intervention at the T2 assessment, favoring the AD-TAR group (AD-TAR: $M = 2.2$, $SD = 1.8$, AD-CS: $M = 1.1$, $SD = 0.7$, $P = .03$).

Additionally, regarding the dwell time, the AD-TAR group observed the nose region significantly longer to recognize joy than the AD-CS group at the T2 assessment (AD-TAR: $M = 685\text{ms}$, $SD = 671$, AD-CS: $M = 288\text{ms}$, $SD = 198$, $P = .03$).

Gaze strategies during dynamic FER

Globally, there was no significant difference in eye gaze strategies to recognize dynamic emotions between groups at T1 and T2 (all $P > .05$). See Figure 5. Nonetheless, the AD-TAR group had longer average fixation duration on the nose region for disgust recognition at T1 assessment (AD-TAR: $M = 192\text{ms}$, $SD = 19$, AD-CS: $M = 165\text{ms}$, $SD = 22$, $P = .03$) and on the eyes' region for sadness recognition at T2 assessment (AD-TAR: $M = 187\text{ms}$, $SD = 14$, AD-CS: $M = 162$, $SD = 24$, $P = .02$) compared to the AD-CS group. At T0, the AD-CS group had a higher number of fixations on the mouth region compared to the AD-TAR group during joy recognition (AD-TAR: $M = 1$, $SD = 0.9$, AD-CS: $M = 2.2$, $SD = 1.2$, $P = .04$), but this difference was not observed at the T1 and T2 assessments (all $P > .05$). The AD-TAR group made significantly more fixations on the nose region for the recognition of joy, fear and neutral condition (all $P > .05$). Additionally, the AD-TAR group spent significantly more time observing the nose region to recognize fear (AD-TAR: $M = 402\text{ms}$, $SD = 174$, AD-CS: $M = 175\text{ms}$, $SD = 121$, $P = .02$) compared to the AD-CS group.

BPSD and Caregiver Burden

The level of BPSD, as indicated by the NPI total score, was significantly lower in the AD-TAR group compared to the AD-CS group at both T1 and T2 assessments (all $P < .05$). Specifically, the AD-TAR group exhibited significantly lower levels of agitation, depression, appetite disorders, and anxiety compared to the AD-CS group at T1 (all $P < .05$).

These significant differences were not observed at the T2 assessment, except for anxiety (AD-TAR: $M = 2.1$, $SD = 2.5$, AD-CS: $M = 5.6$, $SD = 2.9$, $P = .006$). Additionally, at the T2 assessment, the AD-TAR group showed significantly lower levels of apathy and irritability than the AD-CS group (all $P < .05$).

The level of caregiver burden was similar between the groups after the interventions (all Zarit scores $P > .05$).

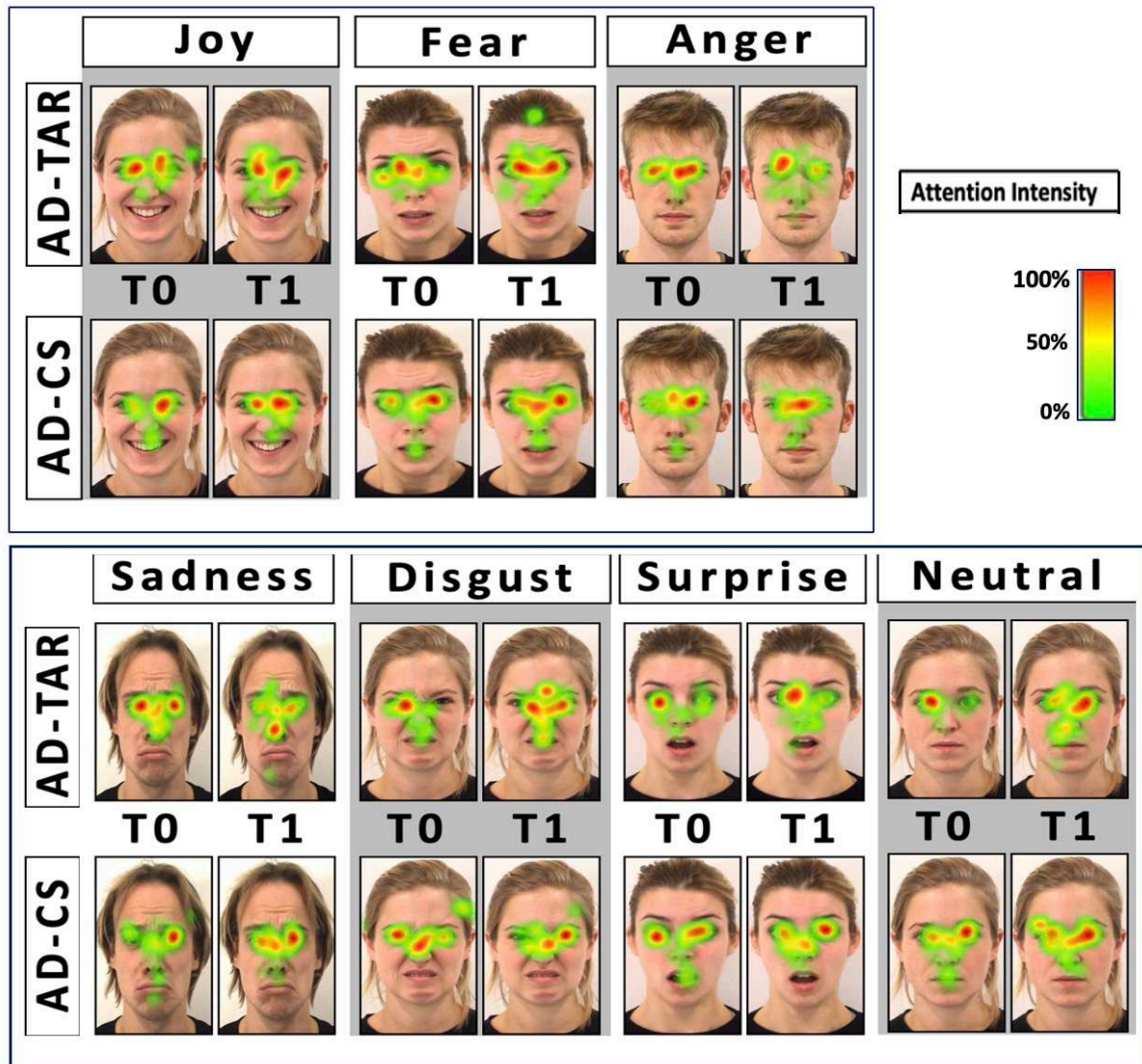


Figure 5. Heat-maps obtained for dynamic FER of each group and each emotion. There were no significant differences neither for pre- and post-intervention nor for between-groups analysis. AD, Alzheimer's Disease; TAR, Training of Affect Recognition; CS, Cognitive Stimulation.

Performances evolution within each group

Within group comparisons, for each group, are shown in table 6 to table 9 and in figure 4 to 6.

Global cognition

The MMS-E scores remained stable across the different assessments in both groups (all $P > .05$).

FER performances

Performance for static FER

AD-TAR group. Compared to T0, there was a significant increase in the total score of Ekman's Faces test and a significant decrease in mean response time at the T1 assessment. These differences were still significant at T2 compared to T0 (all $P < .05$). Especially there was a significant increase in the FER score for sadness and neutral condition at the T1 assessment compared to T0 (all $P < .05$). This improvement in sadness recognition remained significant at the T2 assessment compared to T0 (T0: $M = 1.2$, $SD = 1.1$, T2: $M = 2.6$, $SD = 1.4$, $P = .02$) T1 vs T2 comparisons showed a significant improvement in surprise recognition (T1: $M = 2.4$, $SD = 1.2$, T2: $M = 3.3$, $SD = 0.9$, $P = .05$) and a decrease in sadness recognition (T1: $M = 3.3$, $SD = 1.2$, T2: $M = 2.6$, $SD = 1.4$, $P = .05$). Participants were also significantly faster in recognizing disgust, sadness and neutral condition at T1 compared to T0 (all $P < .05$) and these differences remained significant at T2 compared to T0 for the recognition of sadness and neutral condition (all $P < .05$).

AD-CS group. There were no significant differences between the T0 and T1 assessments in Ekman's Faces Test (all $P > .05$). However, a comparison with T2 was not conducted as the Wilcoxon test was not applicable due to a different sample size at T2 (T0: $N=12$, T1: $N=12$, T2: $N=8$) See *Results, Sample characteristics* and Figure 3.

Performance for dynamic FER

AD-TAR group. FER score remained comparable between T0 and T1, T0 and T2, T1 and T2 assessments (all $P > .05$). Regarding response time, compared to the T0 assessment, participants were globally significantly faster at the T2 assessment (T0: $M = 5.1s$, $SD = 1.1$, T2: $M = 4.7s$, $SD = 1$, $P = .02$), particularly for the neutral condition (T0: $M = 6.3s$, $SD = 1.4$, T2: $M = 5.2s$, $SD = 1.6$, $P = .04$).

AD-CS group. Participants significantly increased their FER score for the neutral condition between T1 and T2 assessments (T1: $M = 2.4$, $SD = 1.3$, T2: $M = 3$, $SD = 1.2$, $P = .04$), with the T2 score remaining similar to the score at T0 (T0: $M = 2.9$, $SD = 1$, T2: $M = 3$, $SD = 1.2$, $P = .43$). Additionally, the AD-CS group was significantly faster in recognizing anger at T1 compared to T0 (T0: $M = 6.3s$, $SD = 1.4$, T1: $M = 5.6s$, $SD = 1.3$, $P = .03$).

Table 6: Within-group analysis for global cognition, facial emotion recognition performances, level of behavioral and psychological symptoms of dementia and level of caregiver burden for AD-TAR group

Mean (sd)	T0	T1	T2	T0 vs T1		T0 vs T2		T1 vs T2	
				V	P	V	P	V	P
MMSE									
N	12	12	12						
Score	20.8 (3.2)	21.3 (3.1)	21.8 (2.8)	13	.52	17	.31	21	.54
Ekman's Faces Test									
N	12	12	12						
Total Score	18.1 (4.8)	21.3 (4.7)	20.4 (5)	4	.02*	5	.02*	32	.28
Mean Response Time	4.4s (1.1)	3.9s (1.4)	3.7s (1.4)	67	.03*	76	.004*	49	.45
Score Joy	3.7 (0.9)	3.8 (0.6)	3.8 (0.6)	0	.35	0	1	1	1
Response time Joy	3.1s (1.5)	3.8s (1.7)	3.2s (2.1)	22	.33	41	.53	47	.23
Score Fear	1.5 (1.2)	2 (1.3)	1.4 (1.2)	23	.39	30	.83	34	.21
Response time Fear	4.2s (1.4)	3.8s (1.7)	3.5s (1.4)	53	.29	52	.11	44	.72
Score Anger	2.8 (1.3)	3 (1.1)	2.8 (1.1)	2	.58	8	1	18	.59
Response time Anger	4.3s (1.4)	4.6s (1.3)	4.2s (1.5)	23	.37	35	.93	53	.29
Score Sadness	1.2 (1.1)	3.3 (1.2)	2.6 (1.4)	0	.004*	2	.02*	25	.05*
Response time Sadness	6s (1.1)	4s (1.6)	4.1s (1.7)	77	.003*	74	.007*	33	.67
Score Disgust	2.8 (1.3)	3.1 (1.4)	3.2 (1.1)	6	.33	8	.15	10	1
Response time Disgust	4.5s (1.3)	3.7s (1.7)	3.6s (1.7)	74	.008*	54	.07	37	.91
Score Surprise	2.9 (1.4)	2.4 (1.2)	3.3 (0.9)	17	.23	16	.43	7	.05*
Response time Surprise	4.2s (1.1)	3.8s (1.7)	3.5s (1.9)	44	.35	52	.10	40	.56
Score Neutral	3.2 (0.7)	3.7 (0.7)	3.3 (1.1)	0	.04*	14	.53	13	.20
Response time Neutral	4.7s (1.8)	3.4s (2)	3.5s (1.7)	61	.01*	76	.005*	32	.97
ADFES									
N	8	8	8						
Total Score	20.4 (6.5)	20.9 (6.4)	19.9 (6.9)	16	.83	14	.53	21	.27
Mean Response Time	5.1s (1.1)	5s (1)	4.7s (1)	22	.62	35	.02*	26	.29
Score Joy	3.5 (0.9)	3.6 (1.1)	3.5 (1.1)	1	1	3	1	1	1
Response time Joy	4.5s (1.4)	4s (0.7)	4.3s (1.5)	20	.35	23	.53	14	.62
Score Fear	2.2 (1.9)	2.2 (1.4)	2.4 (1.7)	7	1	7	.89	7	.89
Response time Fear	4.6s (1)	4.7s (1.3)	4.2s (1.1)	16	.83	30	.11	23	.15
Score Anger	2.2 (1.9)	2.5 (1.3)	2.5 (1.3)	12	.79	3	.42	11	1
Response time Anger	5.7s (1.1)	6.2s (1.4)	5.5s (1.5)	5	.29	17	.67	30	.11
Score Sadness	2.4 (1.3)	2.8 (1.3)	2.2 (1.4)	3	.23	4	.77	16	.28
Response time Sadness	5.8s (1.5)	5.7s (1.2)	5.2s (0.9)	22	.67	23	.53	24	.44
Score Disgust	3.4 (0.7)	2.9 (1.4)	3.1 (1.2)	11	.41	9	.78	3	.43
Response time Disgust	4.4s (1.2)	5s (2.1)	4.1s (1.4)	10	.29	16	.29	32	.06
Score Surprise	3.8 (0.5)	3.4 (0.9)	3.2 (0.9)	8	.34	13	.20	1	1
Response time Surprise	4.2s (1)	3.9s (1.2)	4.1s (1.2)	29	.14	24	.48	8	.35
Score Neutral	2.9 (1.6)	3.5 (1.1)	2.9 (1.6)	0	.37	2	1	6	.17
Response time Neutral	6.3s (1.4)	5.6s (1.3)	5.2s (1.6)	24	.13	33	.04*	27	.23
NPI									
N	12	12	12						
Total Score	22.8 (9.8)	12.2 (10.6)	10.9 (8.3)	63	.01*	77	.003*	37	.36
Delusions	0.6 (1)	0.6 (1.2)	0.3 (0.7)	5	1	8	.35	3	.37
Hallucinations	0 (0)	0 (0)	0 (0)	-	-	-	-	-	-
Agitation/Aggression	0.8 (1.8)	0 (0)	0.3 (0.7)	6	.18	13	.75	0	.17
Dysphoria/Depression	2.8 (3.5)	1 (1.8)	1.1 (2)	23	.15	32	.07	13	.67
Anxiety	4.8 (3.5)	2.8 (1.9)	2.1 (2.5)	45	.09	49	.04*	41	.18
Euphoria/Elation	0.2 (0.5)	0.3 (1.2)	0.5 (1.2)	3	1	3	.58	3	1
Apathy/Indifference	7 (2.5)	2.7 (2.3)	2.2 (2.2)	55	.005*	55	.006*	26	.32
Disinhibition	0.8 (1.1)	0.5 (1.2)	0.4 (1)	5	.41	3	.35	1	1
Irritability/Lability	1.3 (1.4)	1.2 (1.5)	0.4 (0.7)	17	.66	39	.06	14	.14
Aberrant motor	1.9 (2.6)	0.8 (1.4)	1.2 (1.9)	17	.21	7	.58	4	.34
Nighttime behavior	0.9 (2.4)	1.3 (2)	0.8 (1.9)	7	.53	6	1	6	.18
Appetite/Eating	1.6 (2.4)	1.1 (1.7)	1.4 (1.4)	15	.46	11	1	4	.41
ZARIT									
N	12	12	12						
Score	26.6 (12.8)	19.9 (10.7)	17.3 (8.8)	22	.33	52	.01*	59	.12

Variables were compared between each group using the Wilcoxon test. * Significant at $p < .05$

Table 7: Within-group analysis eye gaze behaviors during static and dynamic facial emotion recognition at each assessment for AD-TAR group

Mean (sd)	ROI	T0	T1	T2	T0 vs T1		T0 vs T2		T1 vs T2	
					V	P	V	P	V	P
Ekman's Faces Test										
N										
Total		12	12	12						
Average fixation duration in ms	Face	262 (38)	298 (39)	305 (47)	10	.03*	12	.04*	24	.36
Joy										
Number of fixations	Face	4.7 (1.6)	7.23 (3.5)	5.81 (3.1)	14	.05*	18	.20	58	.15
	Nose	1 (0.5)	2.58 (1.7)	2.25 (1.8)	4	.01*	2	.007*	46	.61
Average fixation duration in ms	Face	246 (59)	291 (43)	292 (60)	12	.04*	14	.05	40	1
Dwell time in ms	Face	1180 (533)	2119 (1134)	1703 (1158)	9	.02*	15	.07	63	.07
	Nose	247 (154)	785 (572)	685 (671)	9	.02*	3	.005*	49	.46
	Mouth	283 (168)	464 (398)	231 (171)	22	.19	49	.46	65	.04*
% Dwell time	Nose	24.1 (18.6)	37.6 (22.2)	39 (16)	11	.06	3	.005*	32	.96
Fear										
Average fixation duration in ms	Face	243 (50)	298 (46)	302 (69)	8	.02*	7	.01*	35	.78
	Eyes	246 (46)	301 (53)	309 (71)	10	.03*	4	.007*	32	.61
Dwell time in ms	Face	1526 (560)	2464 (1206)	2057 (503)	12	.04*	10	.03*	51	.37
	Nose	323 (148)	718 (665)	513 (259)	11	.03*	11	.03*	47	.56
Anger										
Number of fixations	Face	6.1 (1.9)	8.33 (2.3)	7.5 (1.8)	9	.04*	15	.07	56	.21
	Eyes	3.3 (1.7)	4.42 (2)	4.4 (1.5)	19	.23	10	.04*	32	.72
	Nose	1.7 (0.5)	2.8 (0.9)	2.2 (0.9)	0	.002*	6	.06	31	.08
Average fixation duration in ms	Face	260 (29)	302 (46)	315 (56)	5	.009*	6	.01*	27	.37
	Eyes	262 (37)	320 (68)	324 (60)	8	.02*	6	.01*	37	.91
Dwell time in ms	Face	1561 (507)	2555 (1026)	2387 (767)	10	.03*	8	.02*	46	.61
	Eyes	861 (485)	1395 (744)	1448 (624)	16	.08	6	.01*	40	.97
	Nose	442 (172)	847 (422)	640 (254)	0	.004*	9	.02*	59	.13
% Dwell time	Nose	29.9 (11)	33.1 (10.1)	26.7 (7.6)	26	.33	51	.38	72	.01*
Sadness										
Average fixation duration in ms	Nose	246 (56)	265 (55)	297 (81)	12	.04*	9	.02*	20	.15
Dwell time in ms	Mouth	185 (149)	213 (218)	118 (146)	30	.82	48	.20	34	.03*
% Dwell time	Mouth	7.9 (5.7)	9.3 (10.5)	5.7 (6.9)	25	.80	46	.29	34	.03*
Surprise										
Average fixation duration in ms	Face	263 (38)	303 (50)	296 (50)	4	.006*	19	.13	43	.78
	Eyes	271 (45)	325 (70)	322 (96)	14	.04*	23	.22	44	.72
Neutral										
Average fixation duration in ms	Face	270 (39)	306 (58)	309 (53)	25	.29	15	.04*	36	.84
ADFES										
N										
		8	8	8						
Disgust										
Average fixation duration in ms	Nose	186 (55)	192 (19)	161 (22)	11	.36	24	.44	34	.03*

Variables were compared between each group using the Wilcoxon test. * Significant at $p < .05$.

Abbreviations: AD, Alzheimer's Disease; CS, cognitive stimulation; TAR, Training of Affect Recognition; ROI, Region of Interest; SD, standard deviation; V, Wilcoxon test.

Eye tracking Analysis

Gaze strategies during static FER

AD-TAR group. Globally, there was a significant increase in average fixation duration between T0 and T1 assessments, and this difference persisted at T2 (all $P < .05$). Specifically, we observed significant increases in fixation duration for the recognition of fear (in the face and eyes region), anger (in the face and eyes region) and sadness (in the nose region). We also observed a significant increase between T0 and T1 assessments, but without continuity at T2, for recognising surprise (in the face and in eyes region) and joy (in the face). There was a significant increase between T0 and T2 assessments in the face to recognize the neutral condition (all $P < .05$).

Concerning the number of fixations, there was a significant increase in the recognition of joy in the entire face between T0 and T1 assessments. Additionally, there was a significant increase in the nose region at both T1 and T2 assessments compared to T0 for joy recognition. Furthermore, there was a significant increase in anger recognition between T0 and T1 assessments in the entire face and the nose region. Moreover, at the T2 assessment compared to T0, there was a significant increase in the eyes' region for anger recognition (all $P < .05$). Finally, the dwell time in the nose region was significantly increased at T1 and T2 assessments compared to the baseline for recognition of joy, fear, and anger (all $P < .05$). The observation dwell time in the eyes' region was also significantly increased at T2 assessment compared to baseline for anger recognition (T0: $M = 3.3$, $SD = 1.7$, T2: $M = 4.4$, $SD = 1.5$, $P = .04$). Conversely, the dwell time in the mouth region significantly decreased between T2 and T1 assessments for recognition of joy and sadness (all $P < .05$).

AD-CS group. We observed a significant decrease in both the number of fixations and in the dwell time in the eyes' region during disgust recognition (all $P < .05$).

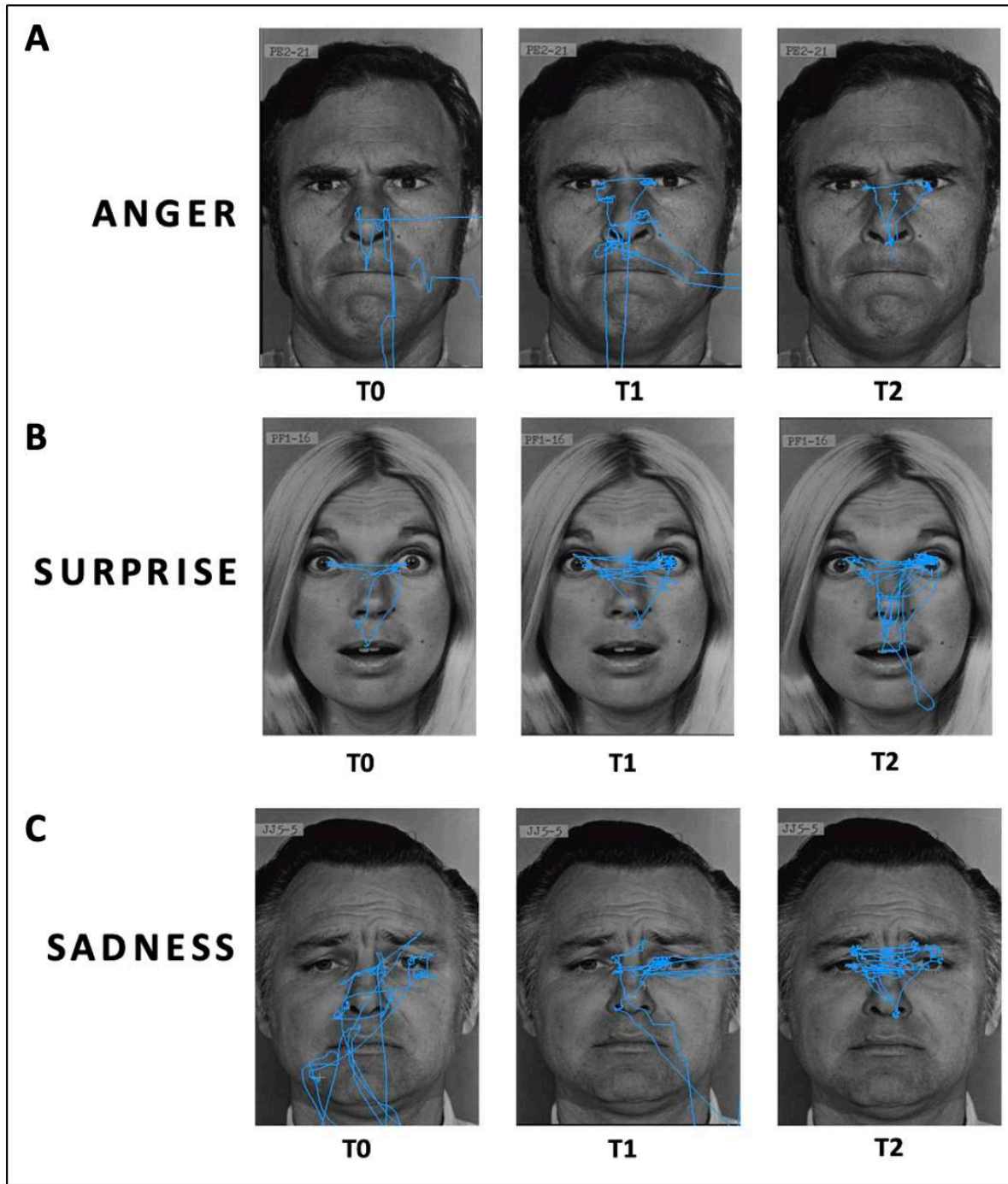


Figure 6. Examples of a visual scan path during static FER of a participant in AD-TAR group before intervention (T0), at the end of intervention (T1) and 1-month post-intervention (T2). **A.** scan path for « ANGER »: participant observed more the upper part of the face in T1 and T2 compared to T0. **B.** scan path for « SURPRISE » and **C.** scan path for « SADNESS »: participant observed more of the upper part and less of the inner part of the face in T1 than in T0; the participant observed again more of the inner part of the face in T2.

Gaze strategies during dynamic FER

AD-TAR group. We noticed a significant decrease in the average fixation duration on the nose region for disgust recognition at the T2 assessment compared to T1 (T1: M = 192ms, SD = 19, T2: M = 161ms, SD = 22, $P = .03$).

AD-CS group. Average fixation duration significantly decreased on the eyes' region for sadness recognition at T2 compared to baseline (T0: M = 190ms, SD = 44, T2: M = 162ms, SD = 24, $P = .04$), and on the nose region for surprise recognition at T2 compared to T1 (T1: M = 171ms, SD = 30, T2: M = 152ms, SD = 32, $P = .02$).

Regarding the number of fixations and the dwell time of the mouth region, they significantly decrease for joy recognition at T1 compared to baseline (all $P < .05$). At T2 assessment, compared to baseline, a significant decrease in the number of fixations and in the observation time of the nose and mouth regions was observed for the recognition of joy, fear, sadness and disgust (all $P < .05$). Finally, a significant decrease in the observation time of the nose region for the recognition of surprise was observed at T2 compared to T1 (T1: M = 341ms, SD = 237, T2: M = 168ms, SD = 95, $P = .04$).

Table 8: Within-group analysis of global cognition, facial emotion recognition performances, level of behavioral and psychological symptoms of dementia and level of caregiver burden for AD-CS group

Mean (sd)	T0	T1	T2	T0 vs T1		T0 vs T2		T1 vs T2	
				V	P	V	P	V	P
MMSE									
N	12	12	8						
Score	20.1 (2.9)	20.4 (3)	22.1 (4.6)	23	.39	na	-	na	-
Ekman's Faces Test									
N	12	12	8						
Total Score	18.2 (4.8)	17.5 (4.2)	18.8 (4.3)	35	.47	na	-	na	-
Mean Response Time	5.2s (0.7)	5.3s (0.9)	4.7s (0.9)	35	.78	na	-	na	-
Score Joy	3.9 (0.3)	3.8 (0.6)	3.9 (0.4)	5	.59	na	-	na	-
Response time Joy	4.4s (1)	4.1s (1.3)	3.6s (0.9)	48	.53	na	-	na	-
Score Fear	1.7 (1.3)	1.4 (0.9)	1.8 (1.5)	19	.48	na	-	na	-
Response time Fear	4.2s (0.9)	5s (1.1)	4s (1.3)	20	.15	na	-	na	-
Score Anger	2.7 (1.4)	2.5 (1.4)	2.5 (1.4)	12	.82	na	-	na	-
Response time Anger	5.6s (1.5)	5.8s (1.4)	5.5s (1.5)	33	.64	na	-	na	-
Score Sadness	1.4 (1)	1.4 (1)	1.9 (1)	18	1	na	-	na	-
Response time Sadness	6.1s (1.2)	6.1s (1)	6.1s (0.9)	43	.78	na	-	na	-
Score Disgust	2.8 (1.1)	2.4 (1.2)	3 (0.9)	43	.40	na	-	na	-
Response time Disgust	6s (1.2)	5.4s (1.5)	4.3s (1.7)	57	.17	na	-	na	-
Score Surprise	2.8 (1.1)	3.4 (0.7)	3.2 (0.7)	6	.10	na	-	na	-
Response time Surprise	4.7s (1.4)	4.8s (1.4)	3.9s (1.1)	38	.97	na	-	na	-
Score Neutral	2.9 (1.2)	2.6 (1.3)	2.5 (1.4)	18	.61	na	-	na	-
Response time Neutral	5.7s (1.2)	5.6s (1.4)	5.2s (1.8)	34	.97	na	-	na	-
ADFES									
N	8	8	8						
Total Score	21.1 (2.9)	21.2 (3.7)	20.8 (4.6)	18	1	16	.87	18	.61
Mean Response Time	5.3s (1.1)	5s (1.1)	5.7s (0.8)	32	.07	15	.73	14	.62
Score Joy	3.5 (0.8)	4 (0)	4 (0)	0	.17	0	.17	na	-
Response time Joy	4.4s (1.4)	3.8s (0.8)	5s (1)	27	.26	10	.29	6	.11
Score Fear	3 (0.8)	3.1 (0.8)	2.4 (1.8)	0	1	16	.28	13	.17
Response time Fear	5s (1.4)	4.6s (1.2)	5.2s (1.3)	28	.18	19	.94	13	.53
Score Anger	2.5 (1.1)	3.2 (1.2)	2.5 (1.3)	0	.05	5	1	9	.27
Response time Anger	6.3s (1.4)	5.6s (1.3)	6.4s (1)	27	.03*	18	1	12	.44
Score Sadness	2.4 (0.7)	2.1 (1.1)	1.9 (1)	14	.59	8	.35	13	.66
Response time Sadness	5.8s (1.3)	6s (1.2)	6.3s (0.6)	15	.72	11	.36	13	.48
Score Disgust	3.2 (1.2)	2.9 (0.8)	3.4 (0.7)	12	.23	2	.77	0	.07
Response time Disgust	5.1s (2)	4.7s (2)	5.6s (1.4)	15	.40	15	.73	11	.36
Score Surprise	3.6 (0.7)	3.5 (0.5)	3.6 (0.5)	9	.77	2	1	2	.77
Response time Surprise	4.2s (1.4)	4.1s (1.4)	5.1s (1.1)	20	.83	4	.06	8	.18
Score Neutral	2.9 (1)	2.4 (1.3)	3 (1.2)	19	.43	4	.85	0	.04*
Response time Neutral	6.4s (0.8)	6s (1.1)	6.2s (1.8)	26	.29	21	.73	16	.83
NPI									
N	12	12	12						
Total Score	25.8 (10.5)	28.2 (11.8)	29.4 (15.6)	15	.22	20	.27	37	.91
Delusions	1.9 (2.8)	2.2 (2.7)	0.7 (1.4)	6	.40	17	.25	26	.06
Hallucinations	0.5 (1.7)	0.5 (1.7)	0.3 (1.4)	na	-	1	1	1	1
Agitation/Aggression	1.7 (1.9)	1.7 (2.4)	1.5 (2)	22	1	20	.83	11	1
Dysphoria/Depression	2.8 (2.4)	2.9 (2.7)	2.3 (3.1)	25	.80	32	.68	24	.44
Anxiety	5.7 (3.1)	5.3 (2.6)	5.6 (2.9)	17	.73	1	1	12	.73
Euphoria/Elation	0.2 (0.6)	0.3 (0.8)	0 (0)	0	1	1	1	3	.35
Apathy/Indifference	5.9 (3.3)	5.2 (3.2)	6 (4.1)	26	.30	10	1	2	.13
Disinhibition	0.3 (0.7)	0.8 (1.2)	0.8 (1.3)	3	.20	2	.17	9	.82
Irritability/Lability	1.7 (2)	1.8 (2.5)	3.6 (3.6)	22	1	16	.13	5	.04*
Aberrant motor	1.7 (1.8)	2 (2.7)	3.3 (3.7)	3	.58	3	.14	2	.27
Nighttime behavior	1.2 (1.7)	1.8 (2.5)	2 (3.2)	14	.62	8	.67	9	.83
Appetite/Eating	2.3 (3.9)	3.8 (2.6)	3.2 (2.7)	6	.11	7	.23	18	.55
ZARIT									
N	12	12	12						
Score	22.4 (12.3)	25.4 (13.6)	21.7 (12.2)	7	.02*	30	.84	67	.04*

Variables were compared between each group using the Wilcoxon test. * Significant at $p < .05$.

Abbreviations: AD, Alzheimer's Disease; CS, cognitive stimulation; TAR, Training of Affect Recognition; na, not available; SD, standard deviation; V, Wilcoxon test.

Table 9: Within-group analysis for eye gaze behaviors during static and dynamic facial emotion recognition of AD-CS group

Mean (sd)	ROI	T0	T1	T2	T0 vs T1		T0 vs T2		T1 vs T2	
					V	P	V	P	V	P
Ekman's Faces Test										
N		12	12	8			na	-	na	-
Disgust										
Number of fixations	Eyes	5.5 (3.6)	4.2 (3)	4.5 (3.1)	49	.03*	na	-	na	-
Dwell time in ms	Eyes	1514 (1162)	1109 (982)	1078 (756)	67	.03*	na	-	na	-
% Dwell time	Nose	25 (15)	33 (17)	29 (17)	12	.04*	na	-	na	-
ADFES										
N		8	8	8						
Joy										
Number of fixations	Nose	2.2 (0.9)	2 (0.6)	1.1 (0.8)	13	.67	28	.02*	33	.05
	Mouth	2.2 (1.2)	1.1 (0.8)	1.4 (1.6)	36	.01*	33	.04*	17	.89
Dwell time in ms	Mouth	501 (376)	223 (138)	229 (270)	36	.01*	33	.04*	14	1
Fear										
Number of fixations	Nose	2.6 (1.9)	1.8 (1.3)	1 (0.8)	30	.10	36	.01*	32	.06
	Mouth	1.7 (1.4)	1.1 (0.8)	0.9 (1.2)	27	.26	36	.01*	27	.26
Dwell time in ms	Nose	522 (501)	332 (241)	175 (121)	29	.14	36	.01*	31	.08
	Mouth	469 (508)	194 (144)	130 (160)	26	.29	36	.01*	27	.23
% Dwell time	Mouth	18 (14)	9 (6)	14 (20)	33	.04*	28	.20	19	.94
Sadness										
Number of fixations	Mouth	1.8 (1.3)	1.2 (0.7)	1 (1.4)	15	.40	36	.01*	24	.48
Average fixation duration in ms	Eyes	190 (44)	166 (28)	162 (24)	24	.44	33	.04*	21	.73
Dwell time in ms	Mouth	393 (361)	228 (160)	160 (229)	25	.36	36	.01*	24	.44
% Dwell time	Mouth	18.9 (22.1)	11.9 (8.3)	11.3 (18.2)	24	.44	35	.02*	23	.53
Disgust										
Number of fixations	Nose	2.3 (0.5)	2.6 (1.6)	1.4 (0.7)	14	.57	28	.02*	30	.12
Dwell time in ms	Nose	386 (131)	433 (267)	243 (103)	14	.62	34	.03*	30	.11
Surprise										
Average fixation duration in ms	Nose	167 (27)	171 (30)	152 (32)	16	.83	26	.33	35	.02*
Dwell time in ms	Nose	273 (172)	341 (237)	168 (95)	10	.29	29	.14	33	.04*

Variables were compared between each group using the Wilcoxon test. * Significant at $p < .05$.

Abbreviations: AD, Alzheimer's Disease; CS, cognitive stimulation; TAR, Training of Affect Recognition; ROI, Region of Interest; SD, standard deviation; V, Wilcoxon test.

BPSD and Caregiver Burden

AD-TAR group. Given NPI scores, the AD-TAR group significantly decreased their BPSD between T0 and T1, and this difference was still present at the T2 assessment compared to T0 (all $P < .05$). Especially, the level of apathy significantly decreased at both T1 and T2 assessments compared to T0 (all $P < .05$). While the level of anxiety also significantly decreased at the T2 assessment compared to T0 (T0: $M = 4.8$, $SD = 3.5$, T2: $M = 2.1$, $SD = 2.5$, $P = .04$). Concerning caregiver burden, the Zarit score had significantly decreased at the T2 assessment compared to T0 (T0: $M = 26.6$, $SD = 12.8$, T2: $M = 17.3$, $SD = 8.8$, $P = .01$).

AD-CS group. In the BPSD, we only observed a significant increase in the level of irritability at the T2 assessment compared to the baseline (T0: $M = 1.7$, $SD = 2$, T2: $M = 3.6$,

SD = 3.6, $P = .04$). Furthermore, the caregiver burden level significantly increased between the T0 and T1 assessments (T0: M = 22.4, SD = 12.3, T1: M = 25.4, SD = 13.6, $P = .02$), and then significantly decreased between the T1 and T2 assessments (T1: M = 25.4, SD = 13.6, T2: M = 21.7, SD = 12.2, $P = .04$), returning to a score close to the baseline (T0: M = 22.4, SD = 12.3, T2: M = 21.7, SD = 12.2, $P = .84$).

4.DISCUSSION

To our knowledge, this is the first study to assess the impact of cognitive intervention on both FER abilities, that is, static and dynamic FER in AD. The aims of this study were threefold: (1) to investigate whether confirm that FER ability could be improved in AD through the implementation of a cognitive remediation program, using both static and dynamic facial expressions as indicators; (2) if improvement was observed, to investigate whether it was associated with changes in visual scanning strategies when perceiving emotional faces; and (3) to examine the effects of this intervention on BPSD and the level of burden experienced by family caregivers.

Our study revealed several key findings: (1) FER ability significantly improved following the cognitive remediation program of FER, and these improvements were sustained over time. This improvement mainly concerned the recognition of static facial expressions (improvement in the score and the speed of recognition), especially for sadness, and to a lesser extent, the recognition of dynamic facial expressions (improved recognition speed); (2) increased FER ability in the AD-TAR group was associated with significant changes in eye gaze strategies when recognizing static facial expressions, and with a reinforcement of eye gaze strategies when recognizing dynamic facial expressions, unlike the AD-CS group for whom a decrease in emotional salience was observed; (3) at the same time, a significant decrease in the BPSD level and caregiver burden were observed for the AD-TAR group.

Beneficial effects of FER ability remediation program in AD

A global improvement in static FER ability was accompanied by a decreased response time in the AD-TAR group following the intervention. These effects were also present at 1-month post intervention, although the performance was no longer significantly superior to the AD-CS group at this stage. These results align with our preliminary study⁴⁷ and with Garcia-Casal, et al.⁵³.

More specifically, the AD-TAR group significantly improved neutral faces recognition. Neutral faces are often seen as expressing ambiguous emotion⁶² and are frequently mislabeled as sadness.⁶³ In AD, studies have indicated impairment in recognising neutral faces.⁶⁴⁻⁶⁶ Some electrophysiological studies analyzing event-related potentials found that vertex positive potential (VPP) and N170 markers are involved in the processing of distinguishing emotional and neutral expressions⁶⁷ and are thought to be generated by the middle fusiform gyrus, the inferior occipital cortex and the superior temporal sulcus.⁶⁸ Other studies have indicated that the amplitudes of N170 were significantly decreased and VPP increased in AD compared to healthy controls.^{66,69} The differences observed in these markers, N170 and VPP, could be explained by a disconnection between posterior regions involved in face processing and prefrontal regions in AD.⁷⁰ In our study, although the remediation program did not specifically focus on neutral faces recognition, it can be hypothesized that training to discriminate between different facial expressions also contributed to distinguishing emotional faces from neutral faces. According to the model proposed by Luo et al.⁶⁷ involving progressive stages of facial expression processing, the distinction between a neutral and an expressive face would precede the accurate recognition of facial expressions. Since discrimination of a neutral face is therefore easier, this may explain the consistent improvement in recognition of neutral faces observed in other studies following FER remediation.^{47,53} Regarding recognizing sadness, as demonstrated in our preliminary study,⁴⁷ a significant improvement was observed following the TAR

remediation. Similarly, in line with other studies, the recognition of the neutral condition and disgust,^{47,53} as well as fear,⁴⁷ showed faster response times. Lastly, consistent with our preliminary findings,⁴⁷ the remediation of FER ability with the TAR program had an adverse effect on the recognition of surprise, with participants frequently misattributing this emotion as fear. However, this effect diminished over time, as the performance in surprise recognition became comparable to that of the AD-CS group one month after the intervention. This finding differs from what was seen in García-Casal et al.'s study⁵³ where surprise recognition was significantly increased following TAR remediation. A possible explanation for these discrepancies could be due to the different assessment tools used to measure FER performances: the Ekman's faces set² in our study compared to the Affect-GRADIOR⁷² employed in García-Casal et al.'s study⁵³. In light of all these results, it would seem that the remediation carried out with the TAR program allows people with AD to better distinguish between neutral faces and expressive faces and to improve the recognition of negative facial expressions (sadness, fear, disgust) whose recognition is impaired in this disease.^{16,72,73}

Our study investigated the maintenance of the intervention's benefits over time by considering outcomes measured at 1 month. Considering the neurodegenerative nature of AD, the follow-up assessment conducted 1-month after intervention (T2), and the observed improvements observed in sadness, fear and the neutral condition (in terms of recognition scores and recognition speed), we can conclude that the beneficial effects of the TAR program are sustained over time. This maintenance could be attributed to the techniques used in TAR program, which have been demonstrated to be effective in individuals with AD, such as errorless learning⁷⁴ and spaced retrieval⁷⁵. However, despite being based on a small sample, our recent 2 years follow-up study of participants from the preliminary study⁷⁶ suggests that the positive impact on FER ability was not maintained over the longer term. Therefore, it would be

interesting to investigate the specific duration of the TAR program's effectiveness in this population.

Regarding dynamic FER, our study did not show a significant improvement in FER performances following the TAR remediation program. The ADFES test was significantly easier than Ekman's faces test at baseline, and after the intervention, FER scores on both tests became similar. This suggests the presence of a ceiling effect for the ADFES test at baseline, which explains the lack of significant evidence of benefit following the intervention. Including a control group of healthy elderly individuals would have allowed us to determine whether the initial performance of dynamic FER was normal, supporting studies indicating that this ability is preserved in the early stages of AD³¹. On the other hand, the AD-TAR group showed a significant improvement in the speed of recognizing dynamic emotions after the intervention. Since the intensity level of facial expression in ADFES is time-dependent, this indicates that participants in the AD-TAR group were able to recognize these emotions at an earlier stage of intensity, which represents a post-intervention benefit. Some studies have demonstrated that the recognition of low-intensity facial expressions is impaired with AD.⁷⁷⁻⁷⁹ Therefore, with the observed post-intervention benefit, our findings support one of the goals of the TAR program, which is to enhance the faster recognition and differentiation of low-intensity expressions. However, further research is needed in individuals with AD using tests that specifically explore different intensity levels of emotions further explore this result. Specifically, our participants showed improved speed in recognizing neutral faces, which may confirm the beneficial impact of the TAR program in distinguishing between neutral and expressive faces, regardless of whether the faces are presented statically or dynamically.

Dynamic FER ability impairment appears to be more established in neurodegenerative diseases such as PD and bvFTD.^{31,80-82} However, in the case of AD, the dynamic FER ability remains a topic of debate due to conflicting findings in the existing literature.³¹

As demonstrated by all these findings, similar to previous studies,^{47,53} our study confirms that FER ability can be rehabilitated in individuals with AD, and the benefits of the intervention are sustained over time. This finding aligns with a recent meta-analysis,⁸³ which showed improvements in recognition abilities in neurodegenerative diseases through three different approaches: cognitive, pharmacological and neurostimulation. Among these approaches, the cognitive approach was found to be the most effective.

FER ability remediation program modifies the way of observing a face expressing an emotion in AD

Studies have consistently shown that individuals with AD exhibit atypical gaze strategies during FER, characterized by reduced observation (both in terms of number and duration of fixations) on the eyes-region and increased exploration of the mouth region.^{10,13,42,84} This atypical gaze behavior may explain the impaired recognition of negative facial expressions in AD, as negative expressions are primarily associated with visual attention directed towards the upper parts of the face, particularly the eyes region.^{45,46} Our study showed a modification of the atypical gaze strategy following cognitive remediation of FER. Indeed, the AD-TAR group showed an increase in average fixation duration during FER on the upper part of the face, particularly on the eye region for fear, anger, surprise, and neutral expressions, and on the nose region for sadness and joy recognition. The average fixation duration corresponds with the cognitive processing of foveal visual information.⁸⁵ The increase in fixation duration on the upper parts of the face suggests a heightened interest in these regions for the purpose of recognizing facial expressions following the TAR program. Other markers of visual interest, such as the number of fixations and observation duration (dwell time), further support the increase in the visual exploration of the upper part of the face for anger (increased in number of fixations and dwell time on the eyes and the nose regions), joy (increased in number of fixations and dwell time on the nose region) and fear (dwell time on the nose region)

recognition. Conversely, there was a decreased interest in the lower part of the face, with reduced dwell time on the mouth region for sadness and joy recognition. These findings are consistent with our preliminary study⁴⁷ and indicate that the TAR program induces a modification in the visual search strategies for emotional cues during FER.

In contrast, the TAR program does not seem to have any effect on visual strategies during dynamic FER, since these remained similar post-intervention for the AD-TAR group. However, in parallel, significant changes in eye-gaze strategies were observed in the AD-CS group, with decreased observation of emotional regions of interest for FER. Specifically, there was a progressive decrease in the average fixation duration for sadness (eye region), and surprise (nose region) recognition and a decrease in the number of fixations and the duration of observation (dwell time) on the nose and/or on the mouth for the recognition of all emotions (except anger) and the neutral condition. These results observed in the AD-CS group can be interpreted as a progressive decrease in the emotional salience of the regions of interest of the face during FER, resulting in reduced attentional capture towards those areas. In contrast, the TAR program appears to have reinforced and maintained an adapted visual exploration while recognizing dynamic facial expressions. It is hypothesized that, at this stage of the disease, the loss of emotional salience was not significant enough to have a noticeable impact on the dynamic emotion recognition performance in the AD-CS group. However, in contrast to the AD-TAR group, it is believed that as the emotional salience of dynamic faces continues to deteriorate over time, the dynamic emotion recognition performance will gradually worsen within the AD-CS group, as observed in the other studies.³²

Visual attention, emotional saliency and eye-gaze strategies

The atypical gaze strategies observed in individuals with AD may be attributed to a different allocation of visual attention towards the most emotional salient facial features.^{42,86} FER ability is a complex process that involves both visual attention, as indicated by scanning

patterns, and higher cognitive abilities, including executive functions, which influence gaze strategies.^{87,88} Two type of attention processes are involved in visual exploration: (1) an early, effortless, and automatic orientation of attention referred to as “bottom-up”, which is driven by the visual characteristics of the stimuli,⁸⁹ and (2) a slower, effortful, and controlled attention process known as “top-down”, which is influenced by the cognitive characteristics of the observer.^{89,90} The frontal eye fields generate voluntary eye movements,^{91,92} which, together with the prefrontal cortex and intraparietal sulcus, constitute the dorsal fronto-parietal attentional network supporting the “top-down” attention directing mechanism.^{93,94} “Bottom-up” visual exploration relies on the ventral fronto-parietal attentional network, composed of the right ventral frontal cortex and the right temporo-parietal junction.⁹⁴ While the dorsal fronto-parietal attentional network is active (attention-demanding tasks), the default mode network becomes inactive, and vice versa.⁹⁵ This network, involved in introspection and emotional processing, posterior cingulate cortex, medial prefrontal cortex, inferior parietal cortex and temporal cortex, shows a greater activity while the individual is at resting-state than at execution of a cognitive task.^{7,96-98} The salience network is another significantly involved network in visual exploration. It is constituted by anterior cingulate cortex, ventromedial prefrontal cortex, insula, striatum and amygdala,⁹⁶⁻⁹⁹ and plays a key role in the identification and direction of attention to the most relevant stimuli in the environment to guide and adapt the behavior.^{7,99-101} All these networks are involved in FER^{95,102,103} and are impaired in individuals with AD.^{7,104-117} The changes in the patterns of observation of emotional faces during the progression of the disease can be attributed to the progressive deterioration of executive and visuo-spatial functioning. This deterioration leads to a disruption of top-down attention mechanisms involved in visual search,^{118,119} resulting in difficulties in selecting relevant information and inhibiting irrelevant information.¹²⁰ AD has been proposed to be a disconnection syndrome¹²¹⁻¹²⁵ characterized by

alterations in the default mode network^{126,127} and the anterior-posterior disconnection.^{69,109,126,128-130}

The fact that the FER ability can be modulated in AD suggests that the impairment of this ability stems from a deficit in directing attention towards emotionally salient regions of the face displaying emotions. In our study, the TAR program led to a shift in attention towards the upper part of the face, enhancing the recognition of negative facial expressions, particularly sadness, which is associated with observing the eye region. However, this shift in attention also resulted in a degradation of surprise recognition, as it requires exploring the entire face.¹³¹

According to these findings of an attentional origin of FER impairment, one study showed that fear recognition in AD can be improved by initially presenting only the upper part of the face and later revealing the entire face, thus directing attention to the eye region.¹³² In healthy subjects, wearing a surgical mask that covers the lower part of the face leads to a decrease in FER, particularly for disgust and joy,^{133,134} which are emotions primarily associated with observing the mouth region.^{45,131} However, this masking effect does not significantly impact fear recognition,¹³³ which is primarily linked to observing the eye region.^{37,45} In our study, the program had a similar "mask effect" by enhancing the recognition of sadness and fear while slightly reducing the recognition surprise. Sadness and fear share similar facial muscle movements¹³⁵ but they differ in terms of their emotional salience configuration. An expression of fear is more closely associated with the eye region than an expression of surprise.^{37,38,45}

Regarding our findings, it can be suggested that the TAR program facilitated enhancements in both "bottom-up" and "top-down" attention orientation mechanisms during FER. The improvement in the static FER was associated with an increased focus on the upper part of the face, particularly the eye region. This region of the face holds the highest emotional salience weight,¹³⁶ which leads to significant attentional capture driven by the amygdala.¹³⁷ The TAR program likely facilitated a rebalancing of salience weights among different facial regions,

with participants' gaze being guided in a bottom-up manner toward the eye region. Additionally, the improvement in the static FER predominantly linked to an increase in the average fixation duration. This suggests that the program enhanced the "top-down" mechanisms involved in searching for facial emotional cues during the recognition of facial emotions, as there is a correlation between average fixation duration and executive functioning during FER.⁴³ Similarly, the results obtained for dynamic FER support similar hypotheses. Due to the presence of motion, dynamic FER can be considered a more bottom-up condition than static FER,¹³⁸ as the successive contractions of the facial muscles more strongly capture attention. This dynamic nature of facial expressions guides attention and provides additional information, making recognition easier.¹³⁹ In contrast to the control group, the TAR program did not result in any modifications of visual exploration patterns or average fixation durations on the salient regions of emotional faces during dynamic FER. This suggests that the TAR program strengthened both the bottom-up and top-down mechanisms involved in searching for emotional information during dynamic FER.

Consequences on BPSD and caregiver burden

A global decrease in BPSD was observed only in the group that received the TAR program. This decrease was maintained even 1-month after the intervention (T2) in comparison to the AD-CS group. Significant reductions were primarily observed in anxiety and apathy levels, followed by decreased agitation, depression, appetite disorders and irritability levels, albeit to a lesser extent. These findings are consistent with the results of our earlier study.⁴⁷ The Beneficial effects observed among participants in the AD-TAR group specifically targeted the most common BPSD observed in AD,¹⁴⁰⁻¹⁴² associated with impaired FER.^{10,143} These effects align with previous studies highlighting the relationship between BPSD and FER deficits in AD. In contrast, the AD-CS group only showed increased irritability levels at T2 compared to baseline. This finding is consistent with research indicating that cognitive stimulation does not

have a positive impact on the behavior of individuals with AD.¹⁴⁴ The concurrent improvement in BPSD and FER ability in the AD-TAR further supports the strong association between behavior and the intactness of social cognition abilities in neurodegenerative diseases.^{51,143} In this context, the TAR program could be considered as a non-pharmacological therapy for managing behavioral disorders.

A decrease in caregiver burden was observed at T2 compared to baseline in the AD-TAR group, whereas Zarit score remained unchanged in the AD-CS group, consistent with the findings of our preliminary study.⁴⁷ These results further support that BPSD^{50,140,141,145} and impaired FER ability^{47,76,146,147} are significant contributors to the burden experienced by family caregivers. The remediation of FER abilities can be considered a therapeutic approach with beneficial effects for both individuals with AD and their family caregivers. It is worth noting that there were no observed beneficial effects on caregiver burden in the AD-CS group, highlighting the potential unique benefits of the TAR program in this context.¹⁴⁸

This current study provides further support for the triple interaction of gaze strategies, FER ability and BPSD in AD, as previously highlighted in studies by Polet et al.^{10,47,84} The TAR program successfully improved FER ability by modifying or reinforcing the gaze strategies, such as favoring the observation of the upper part of the face and increasing the average fixation duration on relevant regions of interest. As a result, there was a reduction in BPSD, including anxiety, apathy, then agitation, depression, appetite disorder, and irritability, leading to a decrease in caregiver burden. In previous studies by Polet et al.,^{10,84} focusing on neurodegenerative diseases, BPSD were associated with a decrease in average fixation duration on the eyes region during the recognition of fear, sadness, and surprise in the case of agitation, for fear recognition in the case of aberrant motor behavior and for joy recognition in the case of appetite disorders. Both BPSD and caregiver burden are two crucial factors in the decision-making process regarding institutionalization in individuals with AD.^{50,140-142,145,149-151} The

positive impact of FER remediation on BPSD, and subsequently on the caregiver burden, could delay the need for nursing home placement. This was evident in our longer-term follow-up study⁷⁶ conducted over a period of 2 years with participants from our preliminary study. It demonstrated that the TAR program had a positive effect on delaying the onset of BPSD, facilitating the continued home care of patients in the AD-TAR group. In contrast, all participants in the AD-CS group required institutionalization. These findings highlight the potential of FER remediation.

Limitations

Firstly, it should be noted that our sample size was relatively small, which necessitated the use of nonparametric statistical methods, as recommended by other authors.^{152,153} Secondly, it is important to acknowledge that the recognition of emotion in the real-world settings involves the integration of multi-sensory information. This includes not only visual cues, as discussed previously but also auditory information, such as prosody.¹⁵⁴ Additionally, the recognition of emotions often relies on the interpretation of bodily signals, including facial and body motions.^{155,156} These signals are embedded in rich interpersonal and social contexts,¹⁵⁴ which further contribute to the complexity of emotion recognition.¹⁵⁷ Some studies have demonstrated that emotion recognition from voice and music remains preserved in individuals with AD.¹⁰⁴ Therefore, future studies should consider more ecologically valid assessments of dynamic FER that incorporate face/body/prosody/social context. Thirdly, the difficulty levels of the FER tests (static/dynamic) used in this study were unequal at baseline, with dynamic presentation being easier than static. To address this bias, it would be beneficial to include a control group of healthy elderly individuals to assess whether FER ability for dynamic mode presentation is impaired and to increase the number of items presented. Furthermore, it is worth noting that there was no control AD group that received no intervention, which would have allowed for the examination of the natural progression of FER ability, BPSD, and caregiver burden in that

condition. Such a control group would also help isolate the specific effects of the FER targeted remediation program, as cognitive stimulation exercises in the control group could indirectly impact FER ability by stimulating attentional abilities.

5.CONCLUSION

This study provides further evidence that FER ability can be enhanced through a cognitive remediation program, and that the benefits of the intervention are sustained over time. Our findings demonstrate that the improvement primarily relates to the recognition of static facial expressions, with a lesser impact on dynamic facial expressions. The enhanced FER ability in the AD-TAR group was accompanied by significant changes in eye-gaze strategies during the recognition of static and dynamic facial expressions and reinforcement of eye-gaze strategies when recognizing dynamic facial expressions. Additionally, the FER targeted remediation program led to a significant decrease in BPSD levels and caregiver burden. These results suggest promising avenues for improving FER ability, which could have positive implications for managing BPSD in both patients and caregivers, potentially delaying the need for institutionalization.

Furthermore, to further investigate the potential of a FER targeted intervention in the prevention of BPSD, it could be interesting to apply such an intervention at the early onset stage of the disease, even before the appearance of significant BPSD. Additionally, these findings are encouraging for combining FER-targeted cognitive intervention with different intervention approaches, particularly neurostimulation or pharmacological interventions.⁸³ It would also be beneficial to extend these interventions to other neurodegenerative diseases such as bvFTD, where BPSD are prominent. Further studies on FER remediation, whether conducted alone or in combination with other approaches, would provide insight into the long-term effectiveness, impact on the family caregivers, and potential delay in institutionalization.

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Conflicts of interest/Funding

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Supplementary material:

Supplementary material 1: CONSORT check list

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7. Supplementary Materials

7.1. Supplementary Material 1

Reporting checklist for randomised trial.

	Reporting Item	Page Number
Title and Abstract		
Title	#1a Identification as a randomized trial in the title.	Section Title
Abstract	#1b Structured summary of trial design, methods, results, and conclusions	Section Abstract
Introduction		
Background and objectives	#2a Scientific background and explanation of rationale	Section Introduction
Background and objectives	#2b Specific objectives or hypothesis	Section Introduction
Methods		
Trial design	#3a Description of trial design (such as parallel, factorial) including allocation ratio.	Section Methods
Trial design	#3b Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	#4a Eligibility criteria for participants	Section Methods-Study population
Participants	#4b Settings and locations where the data were collected	Section Methods-Study population

Interventions	#5	The experimental and control interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Section Methods-Study population/Study design
Outcomes	#6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	Section Methods-Outcome measures
Outcomes	#6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	#7a	How sample size was determined.	Section Methods-Statistical Analyses
Sample size	#7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomization - Sequence generation	#8a	Method used to generate the random allocation sequence.	Section Methods-Study Design
Randomization - Sequence generation	#8b	Type of randomization; details of any restriction (such as blocking and block size)	Section Methods-Study Design
Randomization - Allocation concealment mechanism	#9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Section Methods-Study Design
Randomization - Implementation	#10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions	Section Methods-Study Design

Blinding	#11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.	Section Methods-Study Design
Blinding	#11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	#12a	Statistical methods used to compare groups for primary and secondary outcomes	Section Methods-Statistical Analyses
Statistical methods	#12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Section Methods-Statistical Analyses
Results			
Participant flow diagram (strongly recommended)	#13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	Section Results-Sample Characteristics
Participant flow	#13b	For each group, losses and exclusions after randomization, together with reason	Section Results-Sample Characteristics-Figure 3
Recruitment	#14a	Dates defining the periods of recruitment and follow-up	Section Methods-Study Population
Recruitment	#14b	Why the trial ended or was stopped	n/a
Baseline data	#15	A table showing baseline demographic and clinical characteristics for each group	Section Results-Table 1
Numbers analysed	#16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Section Results

Outcomes and estimation	#17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Section Results
Outcomes and estimation	#17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	#18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Section Results- Comparison of difficulty between static and dynamic facial emotion recognition test
Harms	#19	All important harms or unintended effects in each group (For specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	#20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Section Discussion- Limitations
Generalisability	#21	Generalisability (external validity, applicability) of the trial findings	Section Conclusion
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Section Discussion
Registration	#23	Registration number and name of trial registry	Section Methods- Standard protocol approvals, registrations, and patient consents

Other information

Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Section Discussion
Registration	#23	Registration number and name of trial registry	Section Methods- Standard protocol approvals, registrations, and patient consents
Protocol	#24	Where the full trial protocol can be accessed, if available	n/a
Funding	#25	Sources of funding and other support (such as supply of drugs), role of funders	Section Conflicts of interest / funding

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CHAPTER 7 : Article 3 (EYE-TAR (MA) Follow up) Effets à long terme d'une remédiation de la reconnaissance des émotions faciales et de ses conséquences cliniques dans la maladie d'Alzheimer

Long-term effects of rehabilitation of facial emotion recognition and its clinical consequences in Alzheimer's disease

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DONNÉES FONDAMENTALES

Effets à long terme d'une remédiation de la reconnaissance des émotions faciales et de ses conséquences cliniques dans la maladie d'Alzheimer

Long-term effects of rehabilitation of facial emotion recognition and its clinical consequences in Alzheimer's disease

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S. Hesse^a, A. Morisot^{a,c}, A. Pesce^d, E. Galy^b



Résumé :

Objectifs : Menée auprès de personnes atteintes de maladie d'Alzheimer (MA) et leurs aidants familiaux, cette étude explore l'effet à long terme d'une remédiation de la reconnaissance des émotions faciales (REF) et l'impact sur les stratégies d'observation, les symptômes comportementaux et psychologiques de la démence (SCPD) et le fardeau des aidants.

Méthodes : Inclusion des huit couples MA/aidant ayant complété une étude préliminaire dans laquelle les sujets MA avaient bénéficié soit d'une remédiation de la REF (MA-TAR), soit d'une stimulation cognitive (MA-Contrôle). REF, SCPD, mouvements oculaires et fardeau de l'aidant sont réévalués 2 ans après ces prises en charge.

Résultats : Lors de la réévaluation, 4/4 participants MA-TAR vivaient à domicile, 3/3 participants MA-Contrôle étaient institutionnalisés. Il est observé une diminution de 28% des performances de REF pour le groupe MA-TAR (inférieures au niveau pré-remédiation), associée à une augmentation du nombre de fixations oculaires. Le niveau des SCPD similaire entre les groupes, mais d'avantage de troubles de types productif sont relevés dans le groupe MA-Contrôle et d'avantage de troubles anxio-dépressifs dans le groupe MA-TAR. Le fardeau de l'aidant est supérieur au sein du groupe MA-TAR.

Discussion : Il n'y a pas de maintien à long terme des bénéfices de la remédiation de la REF sur les performances de REF, les stratégies de balayage visuel et sur le niveau des SCPD. En revanche, il semblerait que l'apparition des SCPD de type productif ait été décalée dans le temps et que cela ait favorisé le maintien à domicile de ces patients.

Conclusions : La remédiation de la REF semble être une prise en charge intéressante afin de prévenir l'apparition à long terme de SCPD de type productif.

Mots clés : Maladie d'Alzheimer ; reconnaissance des émotions faciales ; remédiation ; symptômes comportementaux et psychologiques de la démence ; fardeau de l'aidant.

Abstract:

Objectives: Conducted in people with Alzheimer's disease (AD) and their family caregivers, this study explores the long-term effect of the remediation of facial emotion recognition (FER) and the impact on visual scanning strategies, behavioural and psychological symptoms of dementia (BPSD), and caregiver burden.

Methods: Inclusion of eight AD/caregiver couples who completed a preliminary study in which AD subjects had received either FER remediation (AD-TAR) or (AD-Control). FER, BPSD, eye movements and caregiver burden are reassessed 2 years after these interventions.

Results: At reassessment, 4/4 AD-TAR participants were living at home, 3/3 AD-Control participants were institutionalized. 28% of decreased FER performances (inferior to pre-remediation level) in the AD-TAR group was observed and associated with an increased number of eye fixations. The level of BPSD was similar between the groups, but more productive-type disorders in the AD-Control group and more anxiety-depressive disorders in the AD-TAR group were observed. Caregiver burden was superior in the AD-TAR group.

Discussion: There is no maintenance of the benefits of FER remediation on FER performance, visual scanning strategies and the level of BPSD in the long term. On the other hand, it would seem that the appearance of the productive type of BPSD was delayed over time and prioritized the home care of these patients.

Conclusions: The remediation of the FER seems to be interesting in in-patient management to prevent the long-term appearance of the productive type of BPSD.

Keywords: Alzheimer's disease; Facial emotion recognition; Follow-up; remediation; behavioural and psychological symptoms of dementia; caregiver burden

1.INTRODUCTION

La reconnaissance des émotions faciales (REF) joue un rôle clé dans la communication et permet de fournir des informations précieuses afin de répondre de manière appropriée aux différentes situations sociales [1]. Six émotions faciales primaires universelles ont été identifiées : joie, peur, tristesse, colère, surprise et dégoût [2].

La capacité de REF se dégrade avec l'avancée en âge et est altérée dans les maladies neurodégénératives dont la Maladie d'Alzheimer (MA), avec en particulier une altération de la reconnaissance des émotions négatives [3-6]. Ce déficit est présent dès les premiers stades et se dégrade progressivement avec l'avancée de la maladie [7].

La REF est dépendante des stratégies d'observation des zones clé du visage (yeux-nez-bouche). La reconnaissance de la joie et du dégoût est majoritairement reliée à l'observation de la bouche, alors que la peur, la tristesse et la colère sont d'avantage reliée à l'observation des yeux, tandis que pour la surprise, l'observation se répartit équitablement entre ces deux zones clé [8-10]. Dans la MA, le déficit de REF des émotions négatives est corrélé à une diminution de l'observation de la région des yeux [11-14].

Une mauvaise REF d'autrui peut engendrer des comportements sociaux inadaptés [9]. Dans la MA, il existe un lien entre déficit de la REF et symptômes comportementaux et psychologiques de la démence (SCPD) [12-17]. De plus, des études ont montré un « triple lien » entre perturbation des stratégies du regard, déficit de REF et SCPD [12-14].

Les SCPD sont fréquents dans la MA [18], notamment l'apathie, l'anxiété et la dépression [19], et sont corrélés au niveau de fardeau de l'aidant familial et au risque d'institutionnalisation [18,20,21]. Une altération de la capacité de REF entraîne également une augmentation du niveau de fardeau de l'aidant familial [22].

Notre étude préliminaire [13] a montré qu'une remédiation de la REF auprès de personnes atteintes de MA permettait d'améliorer leurs performances en modifiant leurs

stratégies de regard par l'augmentation de l'observation de la région des yeux. Cette amélioration était conjointe à une diminution des SCPD et du fardeau de l'aidant. Ces effets bénéfiques étaient maintenus à moyen terme, c'est-à-dire à 1 mois après remédiation.

L'objectif de cette nouvelle étude, nommée « Follow-up » est de suivre à long-terme l'évolution des performances de REF, des SCPD et du niveau de fardeau de l'aidant familial des patients qui avaient bénéficié de la remédiation de la REF, en les réévaluant 2 ans après cette prise en charge.

2.METHODS

2.1. L'étude préliminaire de Polet et al, 2021 [13] :

Les sujets avaient été recrutés parmi les patients suivis au Centre Mémoire du Centre Hospitalier Princesse Grace de Monaco (CHPG). Les critères d'inclusion étaient : diagnostic de MA selon les critères de l'IWG-2 [23], MMS-E ≥ 15 , sujet accompagné d'un aidant familial et dont la participation à un atelier de stimulation cognitive était préconisée. Les critères d'exclusion étaient : anesthésie générale dans les 3 mois précédant l'étude, trouble ophtalmologique ou neurologique empêchant la réalisation d'un examen d'eye-tracking ou de troubles neuropsychiatriques antérieurs au diagnostic de MA.

Ils ont été distribués soit dans le groupe MA-TAR (prise en charge de type remédiation de la REF par le programme « Training of Affect Recognition » (TAR) [24]), soit dans le groupe MA-Contrôle (prise en charge de type stimulation cognitive classique). Le détail des prises en charge est notifié dans l'article de Polet et al.[13]. La durée de la prise en charge était de 6 semaines, à raison de 2 séances d'une heure par semaine, avec des évaluations réalisées à T0, T1 et T2 (c'est-à-dire avant, à la fin, et un mois après la prise en charge).

2.2. Procédure de l'étude Follow-up :

L'étude consiste à réévaluer à long terme (T3) les participants ayant participé à l'étude préliminaire [13], soit 2 ans après la fin de la prise en charge.

Les critères de jugement sont la comparaison des scores obtenus au test des visages d'Ekman [2], au NPI [25] et au Zarit [26], ainsi que la comparaison des stratégies de regard enregistrées pendant le test des visages d'Ekman, entre l'évaluation T2 (réalisée dans le cadre de l'étude préliminaire) et l'évaluation T3.

Le protocole a reçu l'avis favorable du Comité de Pilotage de la Recherche du CHPG et a été conduit conformément aux directives E6(R2) de la Conférence Internationale sur l'Harmonisation pour les Bonnes Pratiques Cliniques [27].

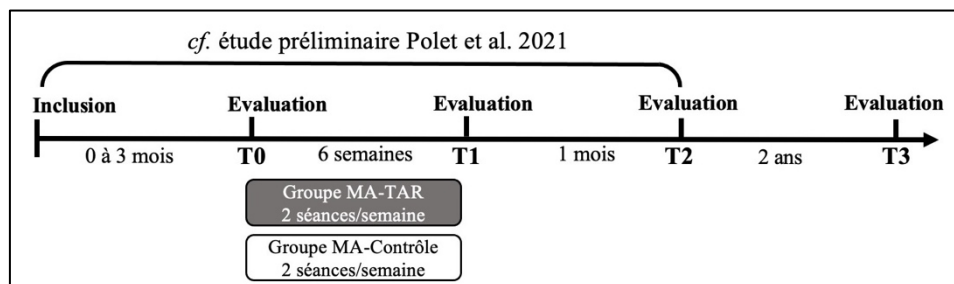


Figure 1. Déroulement de l'étude. MA : maladie d'Alzheimer ; TAR : Training of Affect Recognition

2.3. Participants:

Le recrutement s'est fait parmi les 8 sujets ayant participé à l'étude préliminaire [13].

Critères d'éligibilités : sujet ayant complété l'étude préliminaire [13], accompagné du même aidant, volontaire, pouvant donner son consentement libre, éclairé et écrit. Critères d'exclusion : anesthésie générale dans les 3 mois précédant l'étude, trouble ophtalmologique ou neurologique empêchant la réalisation d'un examen d'eye-tracking.

Le groupe MA-TAR a pu être inclus et évalué dans son intégralité (couple patient-aidant, n=4). Néanmoins le participant N°2 n'a pas pu réaliser le MMSE à T3 en raison de l'altération significative de son état cognitif. Pour le groupe MA-Contrôle, 1 patient n'a pu être inclus (décès), 1 patient et son aidant ont pu être inclus et évalués, et parmi les 2 couples restants seuls les aidants ont pu réaliser les évaluations (un patient ne pouvant pas se déplacer car institutionnalisé dans un département éloigné, et un patient dont le stade cognitif ne permettait plus de réaliser les évaluations).

A T3, 3 participants du groupe MA-TAR était sous traitement anticholinestérasique (participants N°1, 2 et 3) et ce depuis leur inclusion à T0, contre 1 participant du groupe MA-Contrôle (participant N°5).

Les caractéristiques des couples patients-aidants sont présentées dans le tableau 1. Les données MMSE à T2 pour le groupe MA-contrôle sont manquantes en raison de la pandémie de COVID-19 (voir étude préliminaire Polet et al, [13]). Il en est de même pour les données de REF.

L'évaluation à long terme s'est effectuée à 2 ans et 9 mois pour le groupe MA-TAR (T2 : Juin 2019 / T3 : Février 2022) et pour le groupe MA-Contrôle à 2 ans et 1 mois (T2 : Mars 2020 / T3 : Avril 2022).

Tableau 1 : Caractéristiques socio-démographiques des groupes

	Évaluation T0						Évaluation T2			Évaluation T3		
	Sexe	NSC	Nature de l'aidant	Age	MMSE	Lieu de vie	Age	MMSE	Lieu de vie	Age	MMSE	Lieu de vie
Participants MA-TAR	2f/2h	13 (3,7)		69,5 (13,6)	19,8(2,9)		69,5 (13,6)	21 (1,6)		72,5 (13,6)	14 (7,81)	
N°1	f	17	Fils	64	18	Domicile	64	21	Domicile	67	10	Domicile
N°2	h	11	Conjoint	56	19	Domicile	56	19	Domicile	59	NE	Domicile
N°3	f	9	Fille	70	18	Domicile	70	23	Domicile	73	9	Domicile
N°4	h	15	Fille	88	24	Domicile	88	21	Domicile	91	23	Domicile
Participants MA-Contrôles	1f/3h	12,5 (2,6)		71,2 (7)	19,8(1,7)		71,2 (7)	NA		72 (7,5)	NA	
N°5	h	12	Conjoint	63	19	Domicile	63	NR	Domicile	65	14	EPHAD
N°6	h	15	Conjoint	76	20	Domicile	76	NR	Domicile	DCD	NA	NA
N°7	f	9	Conjoint	68	22	Domicile	68	NR	Domicile	71	NE	EPHAD
N°8	h	14	Fille	78	18	Domicile	78	NR	Domicile	80	NR	EPHAD

Note : DCD, décédé ; MA, Maladie d'Alzheimer ; NA, non applicable ; NE, non évaluable en raison de l'altération de l'état cognitif ; NR, non réalisable (à T2 en raison de pandémie COVID-19 ; à T3 patient institutionnalisé dans un département éloigné) ; NSC, Niveau Socio Culturel ; TAR, Training of Affect Recognition ; T2, Suivi 1 mois post prise en charge ; T3, Suivi à long terme 2 ans après la fin de prise en charge.

2.3. Mesures:

Les échelles utilisées et leur mode de passation sont les mêmes que celles de l'étude préliminaire [13] : le MMS-E [28] pour mesurer l'efficacité cognitive globale, les photos de visages issus de la batterie des visages d'Ekman [2] pour la REF, le Neuropsychiatric Inventory (NPI) [25] pour mesurer les SCPD et le Zarit [26] pour le niveau de fardeau de l'aidant. Ces évaluations étaient réalisées en aveugle par un neuropsychologue dédié. Le NPI et le Zarit ont été complétés systématiquement avec le même aidant au cours des différentes évaluations. Les programmes TAR et de stimulation cognitive étaient menés par un autre neuropsychologue.

Les stratégies de regard durant la REF sont étudiées à l'aide d'un eye-tracker (Mobile EyeBrainT2®, SURICOG). Deux caméras infrarouges filment les mouvements des yeux à une fréquence de 300 Hz (précision 0,25° à 60cm de l'écran). Pour chaque photo des visages d'Ekman, nous avons mesuré le nombre et les durées des fixations dans quatre zones d'intérêt : visage entier, yeux, nez et bouche. Une fixation est comptabilisée dès lors que les yeux fixent une zone de 1 degré de côté pendant au moins 100ms [29].

2.4. Analyses statistiques:

Les caractéristiques des participants sont décrites selon leur nature par moyenne et écart type ou effectifs et pourcentages. Elles sont comparées entre le groupe de patient ayant suivi le programme TAR et celui ayant suivi le programme de stimulation cognitive, à l'aide des tests non paramétriques de Fisher (variables catégorielles) ou de Wilcoxon (variables continues). Des comparaisons entre les résultats de l'évaluation T2 de l'étude préliminaire [13] et celle de la présente étude ont également été réalisées à l'aide de tests appariés. Pour les corrélations, le test non paramétrique de Kendall a été utilisé. Le seuil a été fixé à 0,05. Toutes les analyses statistiques ont été effectuées à l'aide du logiciel R version 4.2.0.

3.RESULTS

3.1.Description de la population

A l'inclusion de l'étude préliminaire (T0), les 2 groupes de patients sont appariés en âge (MA-TAR : $m = 69,5$ ans, $sd = 13,6$; MA-Contrôle : $m = 71,2$, $sd = 7$), sexe et en niveau d'étude (MA-TAR : $m = 13$ ans, $sd = 3,7$; MA-Contrôle : $m = 12,5$ ans, $sd = 2,6$) (tous $p > 0,05$ voir [13]). Les scores initiaux sont similaires au MMS-E (MA-TAR : $m = 19,8$, $sd = 2,9$; MA-Contrôle : $m = 19,8$, $sd = 1,7$), aux visages d'Ekman (MA-TAR : $m = 21$, $sd = 2,9$; MA-Contrôle : $m = 16,2$, $sd = 5,4$), au Zarit (MA-TAR : $m = 41$, $sd = 5,3$; MA-Contrôle : $m = 25,2$, $sd = 16,9$), et au NPI (MA-TAR : $m = 22,8$, $sd = 7,1$; MA-Contrôle : $m = 25,8$, $sd = 13,8$) (tous $p > 0,05$; voir [13]).

Compte tenu du décès du participant 6 du groupe MA-Contrôle, nous avons de nouveau vérifié si nos deux groupes étaient appariés au niveau socio-démographique pour l'évaluation T3. L'analyse statistique a confirmé que les 2 groupes étaient appariés en âge (MA-TAR : $m = 72,5$, $sd = 13,6$; MA-Contrôle : $m = 72$, $sd = 7,5$), sexe (MA-TAR : 2h/2f ; MA-Contrôle : 2h/1f) et en niveau d'étude (MA-TAR : $m = 13$, $sd = 3,7$; MA-Contrôle : $m = 11$, $sd = 2,6$) (tous $p > 0,05$).

3.2. Comparaisons intergroupes

A l'évaluation T3, seuls les scores du NPI et du ZARIT ont pu être comparés entre les deux groupes. En effet, pour le groupe MA-Contrôle les données correspondant au MMS-E, à la REF et à l'eye-tracking n'ont été collectées que pour 1 patient.

3.2.1. Troubles du comportement et fardeau de l'aidant :

Les résultats détaillés sont présentés en tableau 2.

A l'évaluations T3, il n'y a pas de différence significative entre les deux groupes pour tous les scores du NPI (tous $p > 0,05$) et pour le score du Zarit ($p = 0,11$). A l'évaluation T2 le niveau de dépression et d'anxiété du groupe MA-TAR était inférieur au groupe MA-Contrôle

($p = 0,04$ et $p = 0,02$, respectivement), ces différences ne sont plus significatives deux ans plus tard à T3 ($p = 0,56$; $p = 0,76$, respectivement).

Tableau 2 : Comparaisons des SCPD et du fardeau de l'aidant entre les groupes MA-TAR et MA-Contrôle pour les évaluations T2 et T3

	Évaluation à T2			Évaluation à T3		
	Groupe	Groupe	p	Groupe	Groupe	p
	MA-TAR n=4	MA-Contrôle n=4		MA-TAR n=4	MA-Contrôle n=3	
Score NPI Total (σ)	7 (4,8)	25,5 (15,5)	0,25	35 (22,1)	33,7 (20,8)	1
Score Idées délirantes (σ)	0,2 (0,5)	1,2 (1,9)	0,51	2,5 (3,8)	1 (1)	1
Score Hallucination (σ)	0 (0)	0 (0)	NA	0,5 (1)	1,3 (2,3)	0,83
Score Agitation (σ)	0,2 (0,5)	0,5 (0,6)	0,61	2,2 (3,9)	4,3 (4,5)	0,58
Score Dépression (σ)	0,2 (0,5)	4,2 (2,9)	0,04	2,5 (3)	0,3 (0,6)	0,56
Score Anxiété (σ)	0,2 (0,5)	5 (2)	0,02	4,5 (3,1)	3 (3)	0,72
Score Euphorie (σ)	0,5 (1)	0 (0)	0,45	0 (0)	1,3 (2,3)	0,39
Score Apathie (σ)	2 (0,8)	5,5 (3,8)	0,31	10 (2,3)	10,7 (2,3)	0,84
Score Désinhibition (σ)	0,5 (1)	0,2 (0,5)	1	2 (2,3)	1,3 (2,3)	0,84
Score Irritabilité (σ)	0,2 (0,5)	3,5 (3,4)	0,12	2 (2,8)	1,7 (2,1)	1
Score Comport. Mot. (σ)	1(2)	3 (3,8)	0,51	3,2 (3,6)	6 (6)	0,72
Score Sommeil (σ)	0,2 (0,5)	1(2)	1	1,2 (1,9)	0 (0)	0,27
Score Appétit (σ)	1,5 (1)	1,2 (1,3)	0,76	4,2 (5,4)	2,7 (2,3)	1
Score Zarit (σ)	22,5 (7,9)	20,5 (12,6)	1	49,5 (15,8)	20,3 (18,2)	0,11

Note : MA, Maladie d'Alzheimer ; NPI, Neuropsychiatric Inventory ; SCPD : symptômes comportementaux et psychologiques de la démence ; TAR, Training of Affect Recognition. Le seuil est fixé à 0,05. Les données de l'évaluation T2 ont été ajoutées à titre de comparaison.

3.3. Comparaisons intra-groupes

Les résultats détaillés sont présentés dans les tableaux 3, 4 et 5.

Rappelons que pour le groupe MA-Contrôle, à T2, en raison de la pandémie de COVID-19, les évaluations MMSE et REF n'ont pas pu être réalisées pour l'ensemble des participants du groupe (voir étude préliminaire [13]).

3.3.1. Fonctionnement cognitif:

Pour le groupe MA-TAR, le score au MMS-E est passé de 21 ($\pm 1,6$) à l'évaluation T2, à un score de 14 ($\pm 7,8$) à l'évaluation T3.

3.3.2. Performances de REF:

Pour le groupe MA-TAR, bien qu'il n'y ait pas de différence significative entre les évaluations T2 et T3 au niveau du score total de REF ($p = 0,10$), ce dernier a tout de même diminué de 28% entre les deux évaluations. En détail (Tableau 3), le score de reconnaissance de la surprise a significativement diminué ($p = 0,03$) et le temps de réponse pour reconnaître la peur, la tristesse et le dégoût avait significativement augmenté ($p = 0,05$; $p = 0,03$; $p = 0,02$, respectivement).

Tableau 3 : Évolution des performances de REF, des SCPD et du niveau de fardeau de l'aidant pour le groupe MA-TAR entre les évaluations T2 et T3

	Groupe MA-TAR		
	T2 n=4	T3 n=4	p T2 vs T3
Score Visages Ekman (σ)	23,5 (1)	17 (5,9)	0,10
Temps rep. Visages Ekman (σ)	3,1s (0,4)	5,4s (1,2)	0,10
Score Joie (σ)	3,8 (0,5)	4(0)	NA
Temps rep Joie (σ)	3,7s (2,5)	4,2s (1,4)	0,78
Score Peur (σ)	2 (0,8)	2,5 (0,6)	0,35
Temps rep Peur (σ)	3s (0,4)	4,9s (1,2)	0,05
Score Colère (σ)	3,2 (1)	2,5 (1)	0,34
Temps rep Colère (σ)	3,1s (0,7)	5,5s (2,7)	0,19
Score Tristesse (σ)	3,5 (0,6)	1,8 (1,7)	0,18
Temps rep Tristesse (σ)	3s (0,7)	6,3s (1,2)	0,03
Score Dégout (σ)	3,8 (0,5)	2,2 (1,1)	0,18
Temps rep Dégout (σ)	2,9s (0,5)	6,6s (1,4)	0,02
Score Surprise (σ)	3,2 (1)	1,5 (1,3)	0,03
Temps rep Surprise (σ)	3,2s (1,2)	4,7s (1,1)	0,09
Score Neutre (σ)	4 (0)	2,5 (1,9)	NA
Temps rep Neutre (σ)	2,7s (0,8)	5,4s (1,2)	0,10
Score NPI Total (σ)	7 (4,8)	35 (22,1)	0,11
Score Idées délirantes (σ)	0,2 (0,5)	2,5(3,8)	0,42
Score Hallucination (σ)	0 (0)	1,3(2,3)	NA
Score Agitation (σ)	0,2 (0,5)	2,2 (3,9)	0,59
Score Dépression (σ)	0,2 (0,5)	2,5 (3)	0,42
Score Anxiété (σ)	0,2 (0,5)	4,5 (3,1)	0,10
Score Euphorie (σ)	0,5 (1)	0(0)	NA
Score Apathie (σ)	2 (0,8)	10 (2,3)	0,10
Score Désinhibition (σ)	0,5 (1)	2 (2,3)	0,37
Score Irritabilité (σ)	0,2 (0,5)	2 (2,8)	0,42
Score Comport. Mot. (σ)	1 (2)	3,2 (3,6)	0,37
Score Sommeil (σ)	0,2 (0,5)	1,2 (1,9)	1
Score Appétit (σ)	1,5 (1)	4,2 (5,4)	0,71
Score Zarit (σ)	22,5 (7,9)	49,5 (15,8)	0,03

Note : MA, Maladie d'Alzheimer ; MMS-E, Mini Mental State-Examination ; NPI, Neuropsychiatric Inventory ; REF : reconnaissance des émotions faciales ; SCPD : symptômes comportementaux et psychologiques de la démence ; TAR, Training of Affect Recognition.; Le seuil est fixé à 0,05.

3.3.3. Stratégies de regard durant la REF :

Toutes émotions confondues, les stratégies d'exploration visuelle sont similaires entre les évaluations T2 et T3 au sein du groupe MA-TAR. Plus en détail (Tableau 4), considérant le temps d'observation, le nombre de fixations et/ou la durée moyenne d'une fixation dans les

zones d'intérêt du visage, il y a une augmentation de l'observation de la région des yeux pour la tristesse (nombre de fixations, $p = 0,03$), une augmentation de l'observation de la région du nez pour la tristesse, le dégoût et la surprise (tous $p < 0,05$), et une tendance à l'augmentation du nombre de fixations sur la bouche pour le dégoût ($p = 0,06$). Aucune évolution significative n'a été observée pour la joie, la peur et la colère (tous $p > 0,05$).

Tableau 4 : Différences significatives des comportements d'exploration visuelle pendant la REF pour le groupe MA-TAR entre les évaluations T2 et T3

	Groupe MA-TAR (n=4)		
	T2	T3	p T2 vs T3
Visage Ekman Total			
Toutes variables confondues			>0,05
Joie			
Toutes variables confondues			>0,05
Peur			
Tps moyen d'observation du visage (σ)	2376ms (318)	3353ms (843)	0,06
Colère			
Toutes variables confondues			>0,05
Tristesse			
Nombre de fixations sur le visage (σ)	7,1 (1,3)	13,4 (1,9)	0,02
Nombre de fixations RI yeux (σ)	4,8(1,1)	8,6 (2,6)	0,03
Tps moyen d'une fixation RI nez (σ)	310ms (37)	260ms (46)	0,02
Dégoût			
Nombre de fixations sur le visage (σ)	6,8(1,4)	13,7(3,4)	0,03
Nombre de fixations RI nez (σ)	2(1,5)	4,9(1,5)	0,005
Temps d'observation RI nez (σ)	587ms (450)	1429ms (689)	0,04
Nombre de fixations RI bouche (σ)	1,1 (1)	2,8(1,4)	0,06
Surprise			
Temps d'observation RI nez (σ)	520ms (179)	990ms (455)	0,04

Note : MA, Maladie d'Alzheimer ; REF : reconnaissance des émotions faciales ; RI, Région d'Intérêt ; TAR, Training of Affect Recognition ; Le seuil est fixé à 0,05.

3.3.4. Troubles du comportement et fardeau de l'aidant :

Pour le groupe MA-TAR entre les évaluations T2 et T3 (Tableau 3), il n'y a pas de différence significative des SCPD ($p > 0,05$). Par contre, une augmentation significative du score au ZARIT est observée à T3, soit 2 ans après la prise en charge ($p = 0,03$).

Pour le groupe MA-Contrôle, afin de faire une analyse intra-groupe, nous avons enlevé les données T2 du participant décédé. L'augmentation des SCPD entre les évaluations T2 et T3

(Tableau 5) n'était pas significative ($p > 0,05$). Aucun changement n'est observé pour le score au Zarit entre le T2 et T3 ($p > 0,05$).

Tableau 5 : Évolution des scores au NPI et au Zarit pour le groupe MA-Contrôle entre les évaluations T2 et T3

	Groupe MA-Contrôle		
	T2 n=3	T3 n=3	p T2 vs T3
Score NPI Total (σ)	24,7 (18,9)	33,7(20,8)	0,18
Score Idées délirantes (σ)	1,3 (2,3)	1 (1)	1
Score Hallucination (σ)	0 (0)	1,3 (2,3)	NA
Score Agitation (σ)	0,7 (0,6)	4,3 (4,5)	0,37
Score Dépression (σ)	4,3 (3,5)	0,3 (0,6)	0,37
Score Anxiété (σ)	4,7 (2)	3 (3)	0,37
Score Euphorie (σ)	0 (0)	1,3 (2,3)	NA
Score Apathie (σ)	4,7 (4,2)	10,7 (2,3)	0,18
Score Désinhibition (σ)	0,3 (0,6)	1,3 (2,3)	1
Score Irritabilité (σ)	3,3 (4,2)	1,7 (2,1)	0,1
Score Comport. Mot. (σ)	2,7 (4,6)	6 (6)	0,37
Score Sommeil (σ)	1 (2)	0 (0)	NA
Score Appétit (σ)	1,3 (1,5)	2,7 (2,3)	0,37
Score Zarit (σ)	18,3(14,5)	20,3(8,2)	1

Note : MA, Maladie d'Alzheimer ; NPI, Neuropsychiatric Inventory ; Le seuil est fixé à 0,05

3.4. Corrélations entre troubles du comportement et reconnaissance des émotions

faciales à T3 :

A l'évaluation T3, dans le groupe MA-TAR, le score au NPI est corrélé négativement au temps moyen d'une fixation sur le visage, et en particulier pour la peur, la colère, la tristesse et la surprise (tous $\tau = -1$; $p = 0,042$). Le score au NPI est également négativement corrélé avec le score de surprise et avec le temps moyen d'une fixation sur la bouche pour cette même émotion (tous $\tau = -1$; $p = 0,042$). Inversement, le score au NPI est positivement corrélé avec le temps réponse de REF, notamment pour le dégoût et la condition neutre (tous $\tau = 1$; $p = 0,042$).

Les corrélations significatives sont présentées dans le tableau 6.

Tableau 6 : Corrélations significatives entre le score total au NPI, les performances de REF et les stratégies d'observation dans le Groupe MA-TAR à T3.

	Groupe MA-TAR à T3		
	Score NPI Total	tau	p
Visage Ekman Total			
	Tps de réponse	1	0,042
	Tps moyen d'une fixation	-1	0,042
Peur	Tps moyen d'une fixation sur le visage	-1	0,042
Colère	Tps moyen d'une fixation sur le visage	-1	0,042
Tristesse	Tps moyen d'une fixation sur le visage	-1	0,042
Dégoût	Tps de réponse	1	0,042
Surprise	Score	-1	0,042
	Tps moyen d'une fixation sur le visage	-1	0,042
	Tps moyen d'une fixation RI bouche	-1	0,042
Neutre	Tps de réponse	1	0,042

Les corrélations ont été étudiées à l'aide du test de Kendall.

Note : MA, Maladie d'Alzheimer ; NPI, Neuropsychiatric Inventory ; REF : reconnaissance des émotions faciales ; RI, Région d'Intérêt ; TAR, Training of Affect Recognition ; ; Le seuil est fixé à 0,05

3.5. Analyse individuelle :

Les résultats sont présentés dans la figure 2.

3.5.1. Fonctionnement cognitif

Dans le groupe MA-TAR, on constate une diminution du score au MMS-E entre les évaluations T2 et T3 pour les participants 1 et 3 et une augmentation pour le participant 4, le participant 2 étant non évaluable en raison de troubles cognitifs trop avancés.

Dans le groupe MA-Contrôle, le participant 5 (le seul ayant pu être évalué) a un score de 14/30.

3.5.2. Performances de REF :

Dans le groupe MA-TAR, on observe une diminution globale des performances avec une perte de 15 points pour le participant 2 (T2 : 24 vs T3 : 9), de 8 points pour le participant 3 (T2 : 24 vs T3 : 16), de 2 points pour le participant 1 (T2 : 24 vs T3 : 22) et de 1 point pour le participant 4 (T2 : 22 vs T3 : 21). Dans le groupe MA-Contrôle, le participant 5 a un score de 17/28 à T3.

3.5.3. Troubles du comportement et fardeau de l'aidant :

Une augmentation importante du score au NPI est observée pour tous les participants du groupe MA-TAR : 61 points pour le participant 2 (T2 : 3 vs. T3 : 64), 32 points pour le participant 3 (T2 : 6 vs. T3 : 38), 12 points pour le participant 1 (T2 : 14 vs. T3 : 26), et 7 points pour le participant 4 (T2 : 5 vs. T3 : 12). Dans le groupe MA-Contrôle, le participant 5 a une augmentation de 7 points (T2 : 3 vs. T3 : 10), 11 points pour le participant 6 (T2 : 38 vs. T3 : 49) et 9 points pour le participant 7 (T2 : 33 vs. T3 : 42).

Concernant le Zarit, on observe aussi une augmentation importante du score pour tous les participants du groupe MA-TAR : 35 points pour le participant 2 (T2 : 20 vs. T3 : 55), 44 points pour le participant 3 (T2 : 23 vs. T3 : 64), 19 points pour le participant 1 (T2 : 33 vs. T3 : 52), et 13 points pour le participant 4 (T2 : 14 vs. T3 : 27). Dans le Groupe-Contrôle, pour le participant 5, on observe une stagnation du score (T2 : 4 vs. T3 : 4) et une augmentation de 22 points pour le participant 6 (T2 : 18 vs. T3 : 40) et une diminution de 16 points pour le participant 7 (T2 : 33 vs. T3 : 17).

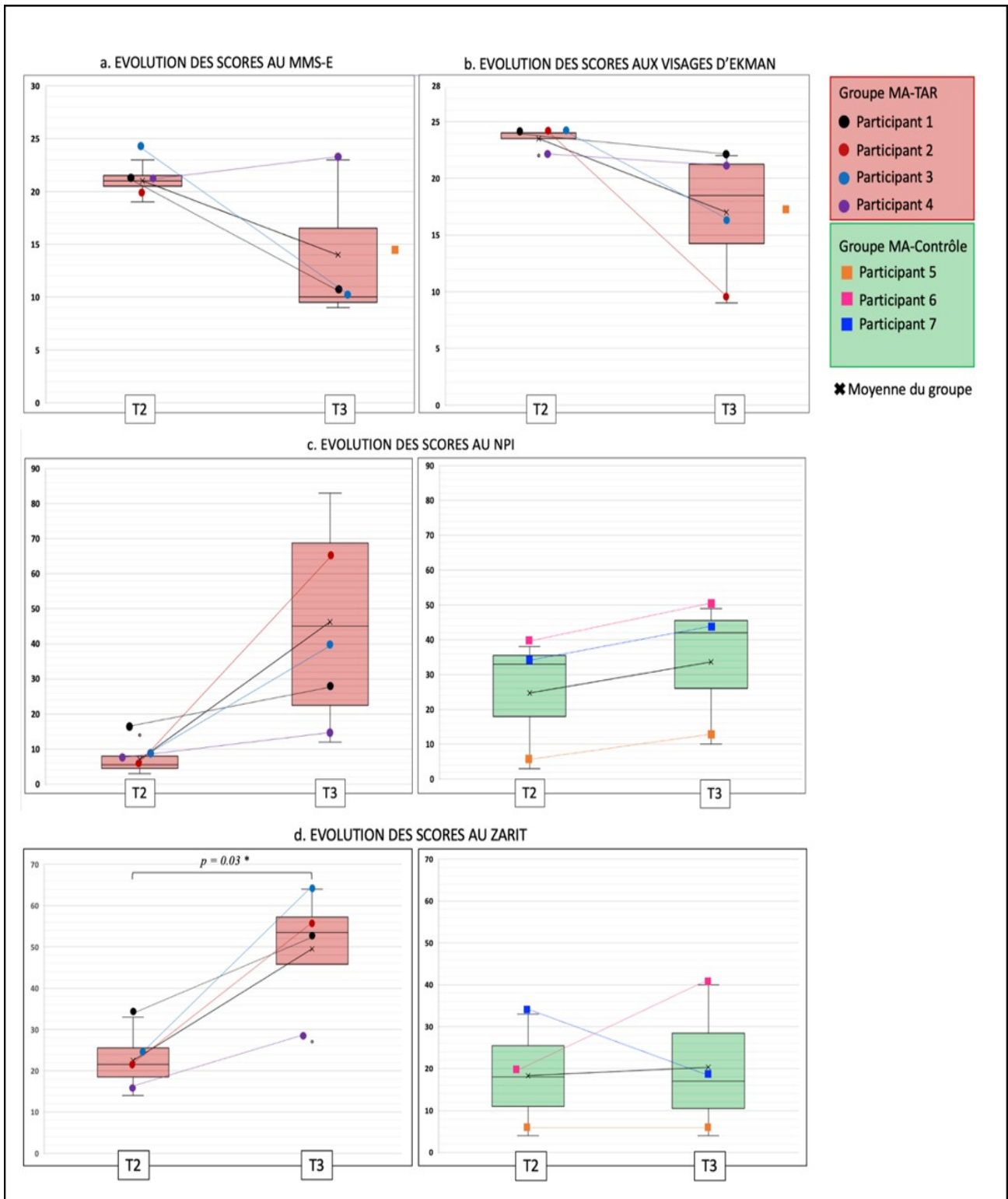


Figure 2. Évolution des scores au MMS-E, aux Visages d'Ekman, au NPI et au Zarit des participants du groupe MA-TAR et du groupe MA-Contrôle entre les évaluations T2 et T3. MA : maladie d'Alzheimer ; TAR : Training of Affect Recognition ; MMS-E : Mini Mental State-Examination ; NPI : Neuropsychiatric Inventory.

4.DISCUSSION

L'objectif de cette étude était de suivre à long terme l'évolution des performances de REF, des SCPD et du niveau de fardeau de l'aidant familial des patients qui avaient bénéficié d'une remédiation de la REF ou d'un programme de stimulation cognitive 2 ans auparavant. Cette évaluation à long terme a montré que (a) pour les deux groupes, il y avait une dégradation des performances de REF ; (b) pour les deux groupes, il y avait une augmentation des SCPD ; (c) le niveau de fardeau de l'aidant avait augmenté au sein du groupe MA-TAR, alors qu'il était resté stable au sein du groupe MA-Contrôle.

La diminution observée des scores de REF n'était pas statistiquement significative. Cependant, d'un point de vue qualitatif, on constatait une diminution de 28 % des performances pour le groupe ayant bénéficié de la remédiation de la REF entre T2 ($23,5 \pm 1$) et T3 ($17 \pm 5,9$), passant ainsi au-dessous du niveau à T0 ($T0 = 21 \pm 2,9$) et obtenant un score moyen similaire à celui du seul participant du groupe MA-Contrôle que nous avons pu évaluer à T3 (score du participant 5 = 17). Ces données semblent indiquer que les effets de la remédiation de la REF sur les performances de reconnaissance s'estompent au cours du temps. Parallèlement au score de REF, le MMS-E a diminué de 33% au sein du groupe MA-TAR entre les évaluations T2 ($21 \pm 1,6$) et T3 ($14 \pm 7,8$). Cette diminution de 7 points au MMS-E en 2 ans et 9 mois paraît légèrement plus importante que ce qui est décrit dans la littérature avec une perte de 2 points au MMS-E en 1 an pour des patients ayant bénéficié d'une stimulation cognitive avec ou sans traitement anticholinestérasique et une perte comprise entre 1.6 et 4 points pour des patients sous traitement anticholinestérasique seul [30-32]. Le contexte de pandémie causée par le COVID-19 durant lequel s'est déroulé l'expérimentation pourrait être une explication à ce déclin cognitif accentué. Également, le fait que, contrairement au groupe MA-Contrôle, la majorité des participants du groupe MA-TAR soit sous traitement anticholinestérasique ait pu contribuer à un déclin cognitif moins important dans ce groupe. La diminution de la

performance de REF et du score au MMS-E dans des proportions similaires est en accord avec les études mettant en évidence que le déclin des capacités de REF est corrélé au déclin cognitif en général [7].

Plus en détail, l'évaluation à long terme a montré que la reconnaissance de l'expression faciale de joie restait préservée au sein du groupe MA-TAR. Ce résultat est en adéquation avec les études stipulant que cette émotion reste bien reconnue dans le vieillissement normal et pathologique [6], et cela indépendamment du score au MMS-E [7]. Inversement, les participants du groupe MA-TAR ont montré une diminution de la reconnaissance de la surprise et une augmentation des temps de réponse pour reconnaître la tristesse, la peur et le dégoût, indiquant que la dégradation de la capacité de REF concerne majoritairement les émotions négatives. Ce résultat est en accord avec l'étude de Virtanen et al. [7] qui met en évidence une corrélation entre déclin du score au MMS-E et dégradation de la capacité à reconnaître des émotions à valence négative.

Concernant les stratégies d'observation des visages émotionnels, les résultats ont été analysés uniquement au sein du groupe MA-TAR (cf. méthodologie). Lors de la reconnaissance de la surprise, nous avons constaté que les participants avaient modifié leurs stratégies de balayage visuel entre les évaluations T2 et T3, en se focalisant désormais sur la région du nez. En parallèle, une diminution significative de reconnaissance de cette émotion était mise en évidence. La reconnaissance de la surprise étant associée à une observation répartie équitablement entre les zones clés du visage (yeux, nez, bouche) chez le sujet sain [8-10], la focalisation du regard sur la région du nez semble avoir influencé négativement la reconnaissance de cette émotion. Par ailleurs, pour la reconnaissance du dégoût et de la tristesse les participants avaient significativement augmenté le nombre de fixations sur le visage, ce qui semble indiquer qu'une plus grande prise d'informations est nécessaire et/ou que la recherche d'informations émotionnellement saillantes est désorganisée pour la reconnaissance de ces

deux émotions. Une autre interprétation est que les modifications des patterns d'observation des visages émotionnels au cours de la progression de la maladie seraient la conséquence de la dégradation progressive des fonctionnements exécutifs et visuo-spatiaux, conduisant à une perturbation des mécanismes top-down de recherche visuelle [33,34], et par conséquent à des difficultés de sélection d'informations pertinente et d'inhibition d'informations non pertinentes [35] pouvant perturber la capacité de REF.

Pour les SCPD, bien que non statistiquement significative, on observait qualitativement une augmentation importante au sein du groupe MA-TAR (+400% entre les évaluations T2 et T3) comparativement au groupe MA-Contrôle (+27%). Parmi les 5 SCPD les plus fréquents, on retrouve pour les deux groupes l'apathie, les comportements moteurs aberrants et les troubles de l'appétit. S'ajoutent l'anxiété et la dépression pour le groupe MA-TAR, et l'agitation et l'irritabilité pour le groupe MA-Contrôle. Il s'agit des SCPD les plus fréquemment observés dans la MA [18,19,,36,37]. Il est intéressant de constater qu'au sein du groupe MA-Contrôle, dont tous les participants sont en EHPAD au moment de l'évaluation T3, les troubles anxio-dépressifs ont diminué (anxiété : -36% ; dépression : -93%) au profit des troubles productifs (agitation : +514% ; comportements moteurs aberrants : +122%). Les SCPD de type productif sont en effet les plus associés à une décision d'institutionnalisation chez les personnes atteintes de maladie neurodégénérative [37]. Pour le groupe MA-TAR c'est une progression importante des scores d'anxiété (+2150%) et de dépression (+1150%) qui est observée entre T2 et T3. Ces patients ont développé davantage de symptômes anxio-dépressifs (tristesse, angoisse lors des séparations avec l'aidant, ...), SCPD responsables d'un fardeau moins élevé pour l'aidant comparativement aux troubles productifs et à l'apathie, et par conséquent moins corrélés à un risque d'institutionnalisation [18-21,36-40]. A l'évaluation T3, le niveau de fardeau des aidants du groupe MA-TAR était 2,5 fois plus important que celui du groupe MA-Contrôle. Dans le contexte de SCPD précédemment décrit, ces résultats semblent contradictoires. Une explication

possible est le fait que, contrairement aux participants du groupe MA-Contrôle, l'ensemble des participants du groupe MA-TAR vivaient toujours à leur domicile à T3, la charge ressentie à ce moment précis par leurs aidants familiaux étant naturellement supérieure à celle d'aidants dont les proches étaient institutionnalisés ressentant donc un niveau de fardeau inférieur [41]. Cela semble indiquer aussi qu'un niveau de fardeau supérieur a probablement été atteint plus précocement par les aidants du groupe MA-Contrôle puisqu'aucun de ces aidants n'a été en mesure de continuer à s'occuper de son proche malade au domicile. Toutefois, même si les SCPD de type productif restaient prédominants dans le groupe MA-Contrôle à T3 comparativement au groupe MA-TAR, une forte progression de ce type de SCPD était également observé au sein du groupe MA-TAR notamment pour l'agitation (MA-TAR : +1000% ; MA-Contrôle : +514%) et pour les comportements moteurs aberrants (MA-TAR : +220% ; MA-Contrôle : + 122%). A la lumière de l'ensemble de ces éléments, une hypothèse possible serait que la remédiation de la REF a pu décaler l'apparition à long terme des SCPD de type productif et par conséquent a eu des effets bénéfiques sur l'aidant familial permettant ainsi de retarder l'entrée en institution.

SCPD et performances de REF étaient négativement corrélés, ce qui a déjà été mis en évidence par de nombreuses autres études [14-16,42]. Par ailleurs, les SCPD étaient également négativement corrélés à la durée moyenne d'une fixation sur le visage lors de la REF. Dans l'étude préliminaire [13], l'amélioration des performances de REF constatée au sein du groupe MA-TAR était conjointe à une augmentation de la durée moyenne d'une fixation sur le visage et à une diminution des SCPD. Ces données semblent donc indiquer que les bénéfices de la remédiation de la REF se sont estompés au cours du temps, notamment au niveau des stratégies d'exploration visuelle des visages, et confirment aussi le « triple lien » entre REF, SCPD et pattern d'observation des visages émotionnels [14].

Cette étude montre qu'il n'y a pas de maintien à long terme des bénéfices obtenus par la remédiation de la REF sur les performances de REF, les SCPD ou encore sur le niveau de fardeau de l'aidant. Il est possible cependant que cette prise en charge ait eu des effets sur le type de SCPD développés au cours du temps. En effet, il y a la mise en évidence de troubles productifs (agitation et irritabilité) plus importants chez les participants du groupes MA-Contrôle. Ces troubles, plus difficiles à gérer pour les aidants, sont une cause d'institutionnalisation. Toute prise en charge pouvant favoriser le maintien au domicile de patients MA auraient des répercussions socio-économiques significatives. En effet, l'entrée en institution affecte négativement l'état psychologique du malade et de sa famille [43-46] et entraîne des coûts importants pour le patient, ses proches et la société [40,44], avec un coût 1,8 fois plus élevé qu'une prise en charge au domicile [47].

A la lecture de nos résultats, il parait pertinent de réaliser une étude longitudinale s'appuyant sur un effectif plus large afin de confirmer les effets à long terme d'une remédiation de la REF sur les délais d'apparition des SCPD productifs avec en corollaire l'institutionnalisation du patient atteint de MA.

Cette étude présente plusieurs limites. Tout d'abord la taille de nos échantillons qui était faible (4 couples patient-aidant dans chaque groupe), à laquelle s'ajoutaient des données manquantes. En effet, pour les patients du groupe MA-Contrôle nous n'avions pas de données à T2 (l'échéance tombant en période de confinement durant la Pandémie de Covid, seules les échelles avec les aidants ont pu être complétées par entretien téléphonique), et/ou à T3 (décès d'un participant, patients non évaluables du fait de troubles cognitifs trop avancés...). Par conséquent, et même si notre méthodologie statistique a été adaptée en utilisant des tests non paramétriques, il est difficile d'extrapoler des conclusions au regard d'échantillons aussi petits et incomplets.

Une autre limite est apparue suite à la non-possibilité d'évaluer certains patients à T2 en raison de leur état cognitif, posant la question d'une inclusion de patients situés à un stade trop avancé de la maladie. L'un des critères majeurs de l'étude étant d'évaluer l'impact de ces prises en charge sur les SCPD, nous avons la contrainte de recruter des patients ayant un niveau cognitif suffisant pour suivre ces programmes et présentant également un certain niveau de SCPD afin de pouvoir mesurer un éventuel effet des prises en charges. Certaines études mettant en évidence une corrélation positive entre stade de la maladie et niveau de SCPD [36], nous avons choisi d'inclure des patients situés à un stade léger-moderé, correspondant à un MMS-E ≥ 15 . Compte tenu des résultats de l'étude, un bon compromis serait donc d'inclure un groupe de participants MA à un stade léger (MMS-E > 20), présentant peu de SCPD, afin de les évaluer deux ans plus tard et de mesurer un éventuel effet préventif de ce type de remédiation sur le développement de SCPD à long terme.

En outre, le délai moyen d'évaluation entre T2 et T3 n'était pas strictement identique entre les deux groupes (2 ans et 9 mois pour le groupe MA-TAR, contre 2 ans et 1 mois pour le groupe MA-Contrôle). Cette différence résultait des restrictions problèmes de disponibilités des patients et de leurs aidants, particulièrement en période de restrictions liées à la pandémie de COVID-19. Compte tenu de la dégradation progressive des capacités cognitives au cours de la maladie [30-32,36], et des liens entre niveau d'efficacité cognitive, SCPD et capacités de REF [7,9,12-17,42], il est possible que ce décalage de 8 mois entre les deux groupes ait pu mener à une légère surestimation du niveau de SCPD et à une légère sous-estimation des capacités de REF au sein du groupe MA-TAR comparativement au groupe MA-Contrôle.

Enfin, l'évaluation des niveaux de SCPD entre les groupes ont également pu être biaisés en raison des conditions d'évaluation différentes, les aidants du groupe MA-TAR vivant toujours avec leur proche malade, contrairement aux aidants du groupe MA-Contrôle. Ces conditions de vie différentes étaient associées à un niveau de fardeau 2,5 supérieur dans le

groupe MA-TAR. Ainsi, le fait de vivre quotidiennement avec le proche malade a pu entraîner une surestimation du niveau de SCPD comparativement aux aidants ne partageant plus le quotidien de leur proche. Néanmoins, les aidants du groupe MA-Contrôle rendaient visite plusieurs fois par semaine à leurs proches et nous avons veillé à ce qu'ils rapportent les éventuels changements de comportements au NPI qu'ils avaient personnellement observés afin de s'approcher au maximum des conditions d'évaluation précédentes.

Pour l'ensemble de ces raisons, nos résultats, bien qu'encourageants, doivent être considérés avec prudence. Une validation de ces données auprès d'une population plus conséquente et intégrant un groupe supplémentaire situé à un stade moins avancé de la maladie est nécessaire.

5.CONCLUSION

Cette étude montre que la remédiation de la REF pourrait avoir des effets bénéfiques à long terme sur les troubles du comportement de type productif chez les personnes atteintes de MA. Couplée aux résultats initiaux [13] ces études pointent l'intérêt de l'utilisation de techniques de remédiation cognitive chez ces patients malgré la problématique neurodégénérative. Une perspective à court terme serait d'étudier les effets de ce type de remédiation cognitive auprès de personnes atteintes de maladies neurodégénératives en général quel que soit le phénotype clinique. Enfin, ce type de prise en charge non médicamenteuse semble être une piste intéressante afin de favoriser le maintien au domicile de ces patients.

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Déclaration de liens d'intérêts

Les auteurs déclarent ne pas avoir de lien d'intérêt.





PART IV: DISCUSSION

CHAPTER 8: DISCUSSION

Based on the “triple link” hypothesis between FER, eye-gaze strategies and BPSD, the thesis studied the short and long-term effects of FER ability remediation in people with AD and their family caregivers.

The first objective was to identify through a literature review the different types of interventions aimed at improving FER ability in NDD, to examine their effects and to screen the most effective and appropriate method in AD.

Our second objective was to confirm, with larger samples, preliminary results obtained from AD participants and their family caregivers following FER cognitive remediation (Polet et al., 2021). This study showed an improvement in FER ability, associated with a change in face-gazing strategies and with a decrease in BPSD and caregiver burden levels in participants who received this remediation. Another objective was also to confirm these results with a more ecological assessment material composed of dynamic facial expressions (in addition to static facial expressions).

Our last objective was to study the long-term effect (> 2 years later) of the cognitive remediation program of FER on people with AD and their family caregivers.

To accomplish these aims, we conducted three studies: “Systematic review and meta-analysis” (**Chapter 5**) for identifying FER-targeted methods in NDD. “EYE-TAR (AD+)” (**Chapter 6**) to confirm the findings of a FER cognitive remediation program, TAR, in a larger sample size by using a more ecological dynamic FER assessment. “EYE-TAR (MA) *Follow up*” (**Chapter 7**) to assess the long-term effect of TAR on people with AD and their family caregivers.

In this chapter, we will summarize and discuss the findings of each study. Then, we will review our study methods. To conclude, we will exhibit the research perspectives and clinical applications resulting from this thesis.

1.SUMMARY OF THE OBTAINED RESULTS

1.1.Can the ability to recognize facial emotions in individuals with neurodegenerative disease be improved? YES!

The systematic literature review has identified interventions used to improve the FER ability in individuals with NDD. And the meta-analysis investigated the magnitude of their efficacy, their impact on BPSD and caregiver burden, as the duration of their effects.

Out of 15 studies included in our systematic review, three types of approaches targeting FER ability in NDD were identified: (1) cognitive approach; (2) neurostimulation approach; (3) pharmacological approach, including single or combined interventions (e.g., pharmacological with neurostimulation). These results associated with the meta-analysis of the included studies show that an approach targeting FER can improve this ability in individuals with NDD. All pooled together, FER-targeted interventions had a significant positive impact with a large effect size.

The cognitive approach was the most effective, with a large and significant effect size in people with AD and HD. This result aligns with studies showing that non-pharmacological interventions may have a greater impact than symptomatic pharmacological interventions (Hempel et al, 2010; Herholz et al., 2013).

Two FER-targeted remediation programs were more specifically used in studies: the TAR program in AD (2 studies) and the METT program in HD (1 study). These cognitive FER-targeted remediations have specific improvement effects, contrary to cognitive-behavioural therapy, schema therapy (Porter et al., 2016), cognitive behavioral analysis system of psychotherapy (Klein et al., 2014), cognitive stimulation therapy (Garcia-Casal et al. 2017) or inpatient psychoanalytic-interactional group therapy (Karparova et al.,2005; Suslow et al., 2004) that do not improve FER ability. These results suggest that the cognitive intervention should be FER targeted to improve this ability specifically.

In AD, fear recognition is challenging, but still when attention is directed towards the eyes (Hot et al., 2013). These findings suggest that FER impairment may have an attentional origin. Similarly, the improvement seen in subjects receiving TAR and METT programs can be attributed to the fact that both rely on FACS (Ekman et al., 2002), a coding system relating a facial expression to a contraction/relaxation pattern of facial muscles, and both consist of explicitly relearning how to observe specific regions of the face. As a result, the remediation approach of these programs aims to improve the ability to recognize facial emotions by providing attentional training.

In AD, following the TAR program, individuals improved neutral condition, disgust, surprise, sadness, and fear (Garcia-Casal et al., 2017; Polet et al., 2021). The latter two facial expressions being less recognized in AD (McLellan et al., 2008; Bediou et al., 2009; Goutte et al., 2011; Elferink et al., 2015; Park et al., 2017). We may suggest that the TAR program not only improved recognition of impaired facial expressions but also allowed discriminating facial expressions often confused (fear/surprise or neutral/sadness) (Edward et al., 2002). In HD, as in AD, individuals show impairment for negative emotions (Johnson et al., 2007; Tabrizi et al., 2009). Following the METT program HD subjects improved the recognition of all emotions, especially the recognition of sadness (Kempnich et al., 2017). In this context, we may suggest that FER-targeted remediation programs efficiently improve impaired facial expressions in these diseases.

Finally, contrary to pharmacological or neurostimulation approaches, no side or deleterious effects have been reported with the cognitive approach in NDD.

The neurostimulation approach has an overall large effect size but without a significant effect on FER ability.

Among all the neurostimulation techniques identified in our review, only Benussi et al. (2020) investigated the tDCS effects on FER ability in individuals with NDD (bvFTD). They

found an improvement in FER performance associated with a decrease in BPSD. This result is in the same line as results obtained using TAR in individuals with AD (Polet et al., 2021). The performances were maintained 6 months post-intervention, which seems superior to results obtained with the cognitive approach TAR. In individuals with depression, treatment using tDCS has a positive effect on both FER ability and thymia (Brenan et al., 2017). And similar results were observed with rTMS, another non-invasive neurostimulation intervention (Berlim et al., 2012). Improvement in FER following tDCS or rTMS was obtained by stimulating the dorsolateral prefrontal cortex (DLPFC) (Berlim et al., 2012; Shutter et al., 2011). This brain region, known for its involvement in emotion processing and the production of depressive symptoms (Padberg & George, 2009; Baeken & De Raedt, 2011), is also involved in top-down emotional control (Cacioppo et al., 1993; Dolcos et al., 2004; Zwanzger et al., 2014). The strong connectivity between the DLPFC and the limbic system, the hippocampus, the amygdala and the subgenual anterior cingulate cortex especially, would explain the improvement in FER ability following DLPFC stimulation (Groenewegen & Uylings, 2000; Kito et al., 2017).

Concerning STN-DBS, only two studies showed a beneficial impact on disgust (Aiello et al., 2014) and fear recognition (Wagenbreth et al., 2019). The other studies showed a deleterious impact of STN-DBS on FER overall, and precisely on fear, sadness, and disgust recognition (Aiello et al., 2014; Kalampokini et al., 2020; Mondillon et al., 2010; Péron et al., 2010; Wagenbreth et al., 2019). This may be due to the surgery micro-lesions' effects (Mulders et al., 2020), causing metabolic changes in brain regions such as STN, thalamus, pallidum, and sensorimotor cortex (Hilker et al., 2008; Pourfar et al., 2009), modifying functioning of the basal ganglia, the orbitofrontal cortex and the fusiform gyrus due to existing connections between these structures (Kalampokini et al., 2020 ; LeJeune et al., 2008 ; Geday et al. 2006), and probably impacting FER since these brain structures are involved in this ability (Kalampokini et al., 2020). Nevertheless, a recent study showed no significant changes in FER

one year after DBS surgery (Duits et al., 2023), indicating that after an initial deleterious effect, DBS does not ultimately seem to alter FER ability in the mid-term.

The pharmacological approach for which the effect size could not be calculated because of insufficient data. However, the systematic review showed heterogenous results.

For example, dopaminergic therapy had positive effect on FER ability in individuals with PD (Dan et al., 2019), in line with results from before 2011 studies not included in our review (Tessitore et al., 2002; Spengelmeyer et al., 2003; Delaveau et al., 2010), but contradictory to other studies claiming that FER impairment is unaffected by medication status in PD (Gray and Tickle-Degnen 2010; Yip et al., 2003; Péron et al., 2009; Cohen et al., 2010; Roca et al., 2010; Enrici et al., 2015). Based on beneficial effects, it seems that dopaminergic therapy partially restores the amygdala response, which is dependent on the disease progression stage (Delaveau et al., 2009). During the initial stages of the disease, the mesocorticolimbic pathways are less affected when compared to the motor pathway (Braak et al., 2004). While dopaminergic therapy improves motor symptoms, it can overstimulate mesolimbic projections to subcortical structures that are involved in emotional processing (Argaud et al., 2018) such as the amygdala, leading to detrimental effects in emotion perception.

Oxytocin had a deleterious effect on anger and fear recognition in individuals with bvFTD (Jesso et al., 2011), and on facial expressions whose recognition was already impaired pre-medication (Oliver et al., 2015). Conversely, oxytocin enhances FER ability in both healthy (Van Ijzendoorn & Bakermans-Kranenburg, 2012; Lischke et al., 2012; Domes et al., 2007; Di Simplicip et al., 2009; Guastella et al., 2010; Marsh et al., 2010) and depressed individuals (MacDonald et al., 2013), due to its action on the limbic system (Insel & Young, 2000). Moreover, in healthy and depressed individuals, oxytocin leads to an increase in the observation of the upper part of the face, whether or not the face expresses an emotion (Andari et al., 2010; Gamer et al., 2010; Gusrella et al., 2008; Vehlen et al., 2023) but without impact on FER

performances in depressed individuals (Vehlen et al., 2023). Conversely, Lischke et al. (2012) found that oxytocin did not affect eye-gaze strategies while resulting in better performance in dynamic FER ability in healthy individuals. These results seem contradictory and incomplete, it would be useful to further dig this field on the NDD population, especially since this molecule has positive effects on BPSD. Based on these findings, oxytocin would be an interesting avenue to investigate.

SSRIs allowed to improve FER ability in individuals with presymptomatic HD (Labuschagne et al., 2013) as seen for bipolar disorder (Vierck et al., 2015) and depression (Shiroma et al., 2014; Tranter et al., 2009). Also, in depression, non-specific anti-depressant pharmacotherapy was found to improve FER ability (Anderson et al., 2011; Naudin et al., 2014), such as reboxetine (Tranter et al., 2009). Conversely, other studies do not show any effect of antidepressants on FER ability in bipolar disorders (Martino et al., 2011; Samamé et al., 2015). This would be another avenue to explore for NDD with studies using both classic and atypical antidepressants.

Atypical neuroleptics deteriorated FER ability in individuals with presymptomatic HD (Labuschagne et al., 2013). However, typical (Hempel et al., 2010) or atypical (Behere et al., 2009) neuroleptics improved FER ability among schizophrenia individuals. Neuroleptics impact the regulation of dopamine in the mesocorticolimbic system, potentially resulting in improved management of amygdala activity and emotional regulation (Salgado-Pineda et al., 2005). Moreover, atypical neuroleptics allowed these individuals to allocate much attention to salient features of the face (eyes, nose, and mouth) (Williams et al., 2003). Given the actual context, additional studies are indicated for the NDD population, especially since these molecules are sometimes used for the treatment of BPSD in NDD.

The combined approach has only been studied in PD with pharmacological (L-dopa) and neurostimulation (STN-DBS) interventions. Only one out of four studies found a beneficial

impact on FER ability (Mondillon et al., 2012). Furthermore, a meta-analysis suggested that the beneficial impact of the combination may be linked to the therapeutic synergism of L-Dopa and DBS effects (Vizcarra et al. 2019). This combination may be effective because it balances the overactivation of the mesolimbic projections towards the amygdala by decreasing activity in the orbitofrontal cortex (Mondillon et al., 2012).

Considering all of this literature review, and given the neurodegenerative nature of the diseases, the cognitive approach seems to be promising based on the fact that its interventions are effectiveness, inexpensive, and do not contain any side effects (Herholz et al., 2013).

Meta-regression analysis showed that female participants had greater improvement of their FER performances following cognitive remediation than male participants. As women generally have better FER abilities (Gonçalves et al., 2018; Olderbak et al., 2019; Quesque et al., 2020), they are likely more sensitive to this type of cognitive remediation than men.

NDD individuals with social cognition impairments and BPSD can lead to caregiver burden (Gregory et al, 2002; Ibañez and Manes, 2012; Kempnich et al, 2018; Polet et al, 2017, 2021; 2022; Martinez et al, 2018; Santamaría-García et al, 2016; Shimokawa et al, 2001; Torralva et al, 2009). Regarding BPSD, three studies were conducted on the effects of cognitive, neurostimulation, and pharmacological approaches in bvFTD and AD patients (Benussi et al., 2020; Garcia-Casal et al., 2017; Polet et al., 2021). These approaches led to decreased BPSD. Moreover, Polet et al. (2021) have shown that this decrease is accompanied by a decrease in the level of caregiver burden.

1.2. What are the impacts of a FER-targeted remediation program in AD? It improves the FER ability and positively impacts the family caregiver!

This second study (EYE-TAR (AD+)) aimed to confirm that FER ability could be improved in AD through a cognitive remediation program, using both static and dynamic facial

expressions as indicators and to confirm the triple link between FER impairment, atypical gaze strategy, and BPSD, all in a larger population.

1.2.1. Beneficial impacts of a FER targeted remediation program in FER ability in people with AD.

The results showed that the TAR, a FER-targeted remediation program, allows to a significantly increase in static FER ability, with effects maintained 1 month after the end of the intervention.

Precisely, an improvement in recognition of sadness, fear, disgust and neutral condition was observed following the intervention. Thus, this program has improved the recognition of facial expressions whose recognition is impaired in AD (Bediou et al., 2009; Hargrave et al., 2002; Drapeau et al., 2009; McLellan et al., 2008; Park et al., 2017). Our results confirm those of our preliminary study (Polet et al., 2021) and those of Garcia-Casal et al., (2017), showing that FER ability can be improved in AD. This also confirms that this type of cognitive remediation initially developed for schizophrenia is also suitable for NDDs. Contrary to the results of Garcia-Casal et al. (2017), the TAR program harmed the recognition of surprise in our study, which is mislabeled as fear, but the follow-up assessment showed that this adverse effect does not persist over time. Also, they showed an improvement of disgust recognition while we observed only a faster response time for this emotion in our participants. The latter result can be explained by different assessments used in these studies: the Affect-GRADIOR (García-Casal et al. 2017b) vs the Ekman's faces set (Ekman, 1976) applied in our study.

The neutral condition was improved commonly in the other studies (Garcia-Casal et al., 2017; Polet et al., 2021). Regarding these results, we may suggest that a FER-targeted cognitive remediation program allows individuals with AD to better distinguish between neutral faces and expressive faces and also to improve the recognition of negative static facial expressions (sadness, fear, disgust, anger) known to be impaired in this disease (McLellan et al., 2008;

Bediou et al., 2009; Fernandez Rios et al, 2021; Goutte et al., 2011; Elferink et al., 2015; Park et al., 2017). Moreover, neutral faces seem to be ambiguous facial expressions (Yoon et al., 2008) and consequently frequently mislabeled as sadness (Edwards et al., 2002). We have also seen that a FER-targeted remediation program contributed to distinguishing emotional faces from neutral faces. Studies show that differentiating emotional and neutral expressions involves the VPP and N170 markers (Luo et al, 2010). The amplitudes of N170 are notably reduced, while VPP is increased in individuals with AD compared to healthy individuals (Saavedra et al, 2012; Fide et al, 2019). The disparity between the N170 and VPP markers might be due to a lack of connection between the posterior regions responsible for face processing and the prefrontal regions in AD (Marinkovic et al, 2000). It would be interesting to compare these markers after the cognitive remediation to see if there was an impact on the reorganization of these networks. According to the model involving stages of facial expression processing of Luo et al., (2010), this step would precede the accurate recognition of a facial expression. This neutral/emotional distinction would thus be easier to process as a training consequence.

Our findings showed that the TAR program did not impact dynamic FER performances. The lack of benefit in the dynamic FER ability could be explained by the possible preservation of dynamic FER ability in our participants, as shown in early-stage AD patients (Goodkind et al., 2015). Also, we observed that ADFES test was significantly easier compared to Ekman's Faces test at baseline, suggesting a ceiling effect for this assessment. Nevertheless, participants who received the TAR program became overall faster at recognizing emotions, which means that they became able to recognize them at a lower level of intensity, that can therefore be interpreted as an improvement. Studies have showed an impairment of low-intensity FER in AD (Jiskoot et al., 2021; Phillips et al., 2010; Sapey-Triomphe et al., 2015). Considering all these findings, we suggest that the TAR program improves dynamic FER by discriminating facial expressions at a lower level of intensity.

To sum up, this current study confirms the previous studies (Garcia-Casal et al., 2017; Polet et al., 2021), showing that FER ability can be improved in individuals with AD by a FER targeted cognitive remediation (Mirzai et al., 2023b), and the beneficial effects are sustained over time. These results may seem surprising given the degenerative nature of the diseases and the memory loss typically associated. But they may be the consequence of techniques that have proved their effectiveness in NDD, such as aid fading (Vallat-Azouvi & Le Bornec, 2013), error-less learning (Clare et al., 2003) and spaced retrieval (Camp et al., 1996), on which the TAR and METT programs are based.

1.2.2. Beneficial impacts of FER targeted remediation program in eye-gaze strategies.

We observed a modification in eye-gaze strategies during FER following the TAR program. The program increased fixation duration on the upper part of the face, especially while recognizing fear, anger, surprise, and neutral expressions and on the nose region for sadness and joy recognition. As we have indicated in **Chapter 2**, for accurate FER, scanning of the eye region is crucial (Smith et al., 2005; Peterson & Eckstein, 2012) except for joy and disgust recognition, where observation of the mouth region is required (Ponari et al., 2012; Guarnera et al., 2017; Calvo et al., 2008; Adolphs et al., 2005; Eisenbarth et al., 2011). These patterns of facial expressions are disturbed in NDD such as AD, bvFTD and PD (Clark et al., 2010; Hutchings et al., 2018; Ogrocki et al., 2000; Polet et al., 2017, 2022). For example, in AD with a shorter dwell time in the scanning of emotional faces and fewer fixations on the eye region (Ogrocki et al., 2000). The TAR program allowed to modify these atypical eye-gaze strategies during FER, that is confirming previous findings (Polet et al., 2021).

Interestingly, the TAR program did not seem to have a beneficial impact on eye-gaze strategies during dynamic FER, the strategies have remained similar post-intervention. However, significant changes in eye-gaze strategies were observed during follow-up assessments in the control group that had received cognitive stimulation with decreased

observation of emotional ROI for FER. We could suggest a progressive decrease in the emotional salience of the face's parts during FER in AD, and that leads to reduced attentional capture towards these regions which progressively disrupts FER. It seems that the TAR program has strengthened and sustained the visual exploration ability while being able to recognize dynamic facial expressions. At this stage, in the group that did not receive TAR, the disturbance of eye-gaze strategies with no impact on the dynamic FER performances could be explained by a non significant emotional saliency loss, that is not enough to impact the performances, or by the presence of compensatory mechanisms that still operating in the mild stage of the disease. However, this group having followed a cognitive stimulation program, so they have been stimulated at attentional level. Consequently, it would have been interesting to compare this decline of attentional capture of the salient emotional zones with a group of AD individuals without any cognitive intervention. Nevertheless, progressive degradation of the dynamic FER ability cannot be ruled out (Martinez et al., 2018). In this sense, it would be interesting to study the comparison with a group of AD participants at a more advanced stage.

1.2.3. So, how about the link between visual attention?

As indicated in **Chapter 2**, visual exploration is guided by bottom-up attention orientation (ventral frontoparietal attentional network) (Corbetta & Shulman, 2002) and top-down attention orientation (dorsal frontoparietal attentional network) (Mesulam, 1985; Corbetta & Shulman, 2002). Furthermore, the salience network is also involved during FER to identify and direct attention to the most relevant stimuli in the environment to guide and adapt the behavior (Multani et al., 2019; Day et al., 2013; Barrett et al., 2013; Menon et al., 2015). Since these networks are impaired in AD (Multani et al., 2019; Drapeau et al., 2009; Ochsner et al., 2004; Possin et al., 2010; He et al., 2007; Sorg et al., 2007; Wang et al., 2007; Gili et al., 2011; Zhou et al., 2015; Hafkemeijer et al., 2015; Weiler et al., 2014; Liu et al., 2014; Binnewijzend et al., 2012; Agosta et al., 2012; Wu et al., 2011), we may think it impairs visual

information seeking strategies, especially during FER by attributing to a different allocation of visual attention towards the most emotional and salient facial features (Ogrocki et al., 2000; Scinto et al., 1994), making difficult to extract emotional information from facial expressions (Garcia-Rodriguez et al., 2012; Hot et al., 2013).

In our study, as well as in our preliminary study (Polet et al., 2021), the TAR program promoted the orientation of visual attention towards the upper part of the face that, resulted in an improvement of recognition of negative facial expressions, especially sadness which is related to the observation of the eye-region (Calvo et al., 2018; Eisenbarth & Alpers, 2011; Schurgin et al., 2014). Our findings are in the same line with Hot et al., (2013), indicating that FER can be improved when attention is oriented towards the eyes. However, this re-orientation of attention caused an impairment of surprise recognition since its recognition requires of the observation of the entire face (Calvo et al., 2018).

We suggest that the TAR program has improved both the "bottom-up" and "top-down" attention orientation mechanisms in FER. Indeed, following TAR: (1) the visual attention is quickly captured towards the upper part of the face, which corresponds to the most emotionally salient region during FER. This implicit reorientation of attention (bottom-up factor) results from the errorless learning implemented during the sessions and is similar to operant conditioning. (2) In parallel with the increased performances, we observed an increased average fixation duration in the regions that capture attention. However, the average duration of fixation is considered as a marker of voluntary information gathering (top-down factor) (Perry & Hodges, 1999).

1.2.4. The “cascading effect” effect on BPSD and caregiver burden.

Our second aim was to study the “cascading effects” of this remediation program on BPSD and caregiver burden. As expected, a “triple link” between modification of eye-gaze strategies, increased FER performances and decreased BPSD was observed following the TAR

program as hypothesized (Polet et al., 2022) and observed in our preliminary study (Polet et al., 2021). Particularly significant decreases in BPSD concerns anxiety and apathy, then agitation, depression, appetite disorder and irritability levels to a lesser extent, all maintained 1 month after the intervention. As indicated in **Chapter 1**, these are the most common BPSD observed in AD (Zhao et al., 2016; Delfino et al., 2021; Schwertner et al., 2022), and they are associated with impaired FER (Kempnich et al., 2018; Polet et al., 2022). These findings reinforce the effectiveness of a specially FER-targeted cognitive remediation program on both improvement of FER ability and BPSD since the cognitive stimulation did not have a positive impact on BPSD within the other group (increased irritability at T2 compared to baseline). This finding confirms the literature on the inefficacious of cognitive stimulation on BPSD in individuals with AD (Carbone et al., 2022). Thus, these findings represent a strong argument for a link between social cognition and behaviors which is an important topic of debate in neuropsychology.

Furthermore, Polet et al., (2021) found that an improvement of FER ability was correlated with a decrease in BPSD and caregiver burden. These results confirm a link between impaired FER ability, BPSD (Gregory et al., 2002; Ibañez & Manes, 2012; Kempnich et al., 2018; Polet et al., 2022; Santamaría-García et al., 2016; Torralva et al., 2009) and caregiver burden (Brown et al., 2018; Cheng, 2017; Elferink et al., 2015; McCade et al., 2013; Miller et al., 2013; Narme et al., 2017; Phillips et al., 2010; Polet et al., 2021, 2022).

Conjointly to the decrease in BPSD, the level of caregiver burden decreased, confirming the previous findings (Polet et al., 2021). These findings are in the same line with the literature indicating that BPSD are the major factor of caregiver burden (Finkel et al., 1996; Andrieu et al., 2003; Bouoleau-Bretonnière & Vercelletto, 2009). Furthermore, they support that BPSD (Boutoleau-Bretonnière & Vercelletto, 2009; Zhao et al., 2016; Delfino et al., 2021; Terum et al., 2017) and impaired FER ability (Greve et al., 1994; McCade et al., 2013) are the main

factors in the burden experienced by family caregivers. However, our results are not exactly similar to our preliminary study, since we mainly reduced anxiety and apathy whereas a decrease in productive BPSD (mainly irritability) was observed in the preliminary study. The productive BPSD are the ones that associated with a lower level of FER and a greater disturbance of gaze strategies (Polet et al., 2022), as well as with a higher level of family caregiver burden (Polet et al., 2022; Zhao et al., 2016; Terum et al., 2017). Nevertheless, the initial average level of productive BPSD was low within our study groups, which probably did not allow us to highlight this effect. Furthermore, the remediation had a positive effect on anxiety, a disorder associated with FER impairment (Horley et al., 2004) and on apathy, which are also major source of caregiver burden (De Vugt et al., 2006; Cheng, 2017). As a result, we can hypothesize that this type of cognitive remediation would lead to better outcomes in patients for whom productive BPSD are at the forefront.

In some way, acting on FER ability resulted in an improvement in communication abilities between patient and caregiver (Kordsachia et al., 2017) and consequently, the relationship between them improved (Carton et al., 1999; Kornreich et al., 2002; Hofer et al., 2009; Janssens et al., 2012; Kordsachia et al., 2017).

1.3. Are the short-term positive impacts maintained in the long term? No, but the long-term consequences can still be considered positive.

This third study (EYE-TAR (MA) *Follow-up*) aimed to explore the long-term effects of the FER remediation program by assessing over 2 years.

1.3.1. How was the evolution of FER performances?

A 28% of the decrease in FER performance was observed in the group that received the TAR program 2 years ago, thus passing below the baseline level and obtaining a similar mean score with the only participant that we could evaluate from the cognitive stimulation group.

These findings suggest that the short-term positive evanesced over time. It was noticed that there was a 33% reduction in the overall cognitive level globally. There seems to be a correlation between the degradation of FER performances and global cognition degradation, consistent with studies that indicate that the impairment of REF results from the degradation of global cognition efficiency (Virtanen et al., 2017; Brandt et al., 2023). Specifically, the group that participated in the TAR program experienced a decrease of 7 points on the MMS-E test within 2 years and 9 months. This decrease seems important compared to the existing findings that found a diminution of 2 points at MMS-E in 1 year receiving a cognitive stimulation program with or without anti-cholinesterase treatment, and a diminution of 1,6 to 4 points for individuals only under anti-cholinesterase treatment (Germain et al., 2019; Requena et al., 2006; Xu et al., 2022). A possible explanation for this accelerated cognitive decline among our participants can be attributed to the context of the COVID-19 pandemic and the successive confinements that took place during this monitoring period, which have resulted in increased BPSD (Barguilla et al., 2020) and accelerated cognitive decline (Li et al., 2023) in individuals with NDD.

Particularly, we observed that recognition of joy was still preserved in the group that received TAR program. This result is in line with the literature indicating that this facial expression is preserved in AD (Chiu et al., 2016; Guaita et al., 2009; Hot et al., 2013; Maki et al., 2013; Martinez et al., 2018; Narme et al., 2013; Ostos et al., 2011) independently to the score in MMS-E (Virtanen et al., 2017). Conversely, we observed a decreased performance for surprise recognition and a slower response time for negative facial expressions. This is in line with the previous findings that have shown the correlation between the decline in cognitive function and the decline in recognition of negative facial expressions (Virtanen et al., 2017).

1.3.2. Is the modification of eye-gaze strategies maintained?

The eye-gaze strategies could only be analyzed in the group that received TAR program. Compared to the end of FER remediation, we observed that there was a modification in visual scanning of expressed faces by focusing mostly on the nose region that resulted in decreased recognition of surprise for which a global scanning of ROI is needed (Calvo et al., 2008; Chaby, 2012; Schurgin et al., 2014). Furthermore, an increased number of fixations on the face was observed in recognition of disgust and sadness, potentially indicating that research of information is needed or a disorganization of emotionally salient information to recognize these facial expressions. Moreover, compared to the baseline, we observed a 265% of increase in dwell time on the nose region for the recognition of surprise and the participants looked more the lower part of the face to recognize disgust, indicating less efficient search strategies than those initially observed 2 years earlier. Based on these findings, (1) there is a loss of benefit following TAR, with the gaze now focusing on the nose region (as if the gaze had "gone down a floor"); (2) searching for facial clues deteriorates over time and seems more random with an increase in the number of fixations, indicating both a modification of attentional capture (bottom-up) and visual information intake strategies (top-down).

1.3.3. What about BPSD and caregiver burden?

We observed an important difference in the evolution of BPSD between two groups: a 400% increase in BPSD in the group receiving the TAR program compared to the group receiving classical cognitive stimulation, in which the increase was 27%. In both groups, we found apathy, aberrant motor behavior, and eating disorders, adding anxiety and depression in the group that received the TAR program, and agitation and irritability in the group that received classical cognitive stimulation. These are the BPSD frequently observed in AD (Zhao et al., 2016; Delfino et al., 2021; Cerejeira et al., 2012; Schwertner et al., 2022). Especially depression, anxiety, and apathy are the first and most frequent BPSD in the early onset of AD,

other BPSD, such as agitation and irritability, appear as the disease progress (Laganà et al., 2022). This follow-up assessment allowed us to observe that the participants who received the TAR program were at home whereas other participants were in nursing home placement. Moreover, we noted an important increase in depression and anxiety levels, which are less correlated to institutionalization than productive BPSD and apathy (Zhao et al., 2016; Delfino et al., 2021; Cerejeira et al., 2012; Schwertner et al., 2022; Chan et al., 2003; de Vugt et al., 2003; Dufournet et al., 2019). Consequently, we observed a higher caregiver burden (2,5 times more) in the group who received the TAR program. Based on these findings, we assert that the participants from the classical cognitive stimulation group would have developed productive BPSD earlier, which engendered a faster placement in the institution. In parallel, we observed that productive BPSD began to appear in the group that received the TAR program, it could be interesting to follow the evolution of these BPSD in these participants. In conclusion, we suggest that a FER-targeted remediation program would delay the appearance of productive BPSD and then lead to delayed institutionalization.

2.THEORETICAL IMPLICATIONS

Our research showed that **the cognitive remediation approach** is the most effective in improving FER ability in NDD. It led to a modification of eye-gaze strategies, allowed to improve the FER performances, decrease the BPSD and, consequently, decrease the caregiver burden, confirming our preliminary results which suggested “cascading effect” at short term and long term. These results revolt several questions and allow us to investigate new avenues to act in different dimensions. In this part, we will discuss the short- and long-term effects of a FER-targeted cognitive remediation program on three dimensions: (1) patient; (2) family, and (3) society, as illustrated in Fig.1.

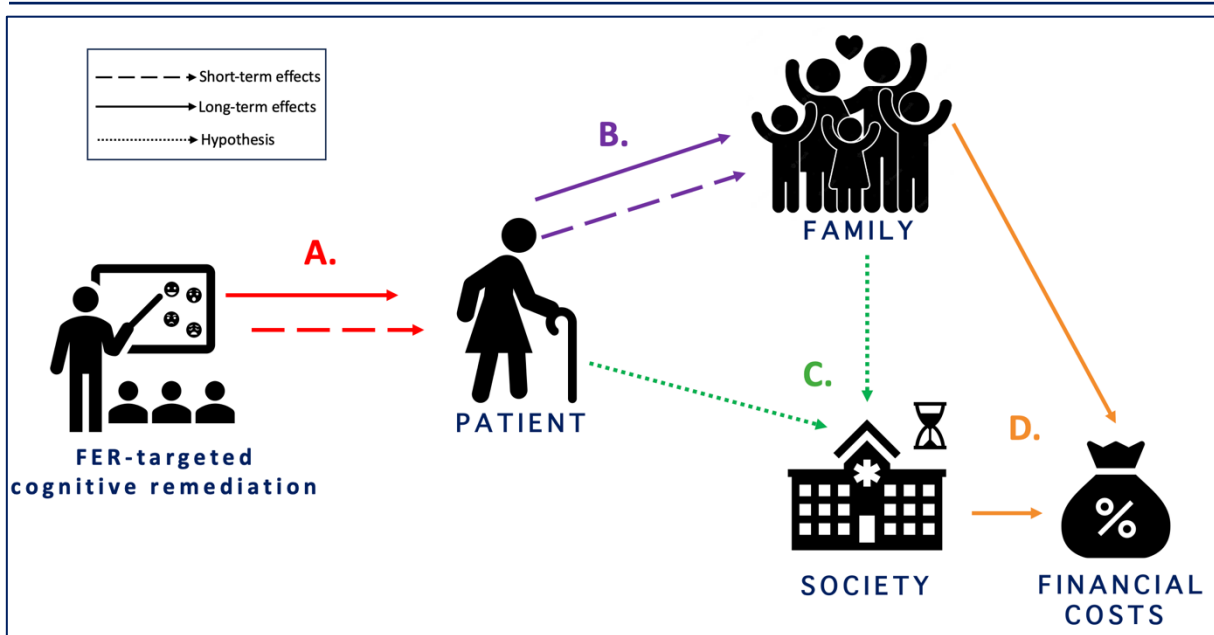


Fig. 1. Representation of the effects of FER-targeted cognitive remediation on individuals with NDD and their environment, **A.** FER-targeted cognitive remediation improves FER ability in individuals with NDD, **B.** This beneficial effect is associated with a decrease in BPSD, which has a lasting positive impact on the quality of life of the family caregiver, **C.** Improvement of FER, reduction of BPSD and the level of burden of family caregivers would lead to delay institutionalization, **D.** and can lead to a significant reduction in financial costs for both society and the family.

2.1. Why and how FER ability can be improved in NDD ??? and why is the FER ability an interesting target for the management of BPSD?

FER ability does not depend on a specific brain structure, but rather relies on a set of key brain structures, themselves involving other brain structures considered secondary, distributed throughout the brain and connected in different brain networks, grouped together in a “super network” called the social brain network (Kennedy & Adolphs, 2012). The fact that social cognition is such a distributed ability makes it very vulnerable to brain damage (Travers et al., 2012; Ameis & Catani, 2015). That is why social cognition impairments are frequent in psychiatric and neurological pathologies (Bertoux, 2022).

We have seen that improvement of FER ability is possible in diseases with severe FER ability impairment, such as schizophrenia (for example: Drusch et al., 2014; Wölwer and Frommann, 2011) or in patients with pure lesion of a key brain structure involved in FER ability

like patient S.M. who suffered bilateral amygdala destruction (Adolphs et al., 2005). In such cases FER improvement was seen when attention was explicitly guided to the eyes (Drusch et al., 2014; Adolphs et al., 2005). In NDD, such as AD similar results were obtained (Hot et al., 2013). Regarding these findings, FER impairment would therefore result from an impairment of the mechanisms for seeking visual emotional information on the face.

The visual scanning starts by being guided immediately by “bottom-up” attentional orientation (rapid and automatic) to the most salient stimuli (Theeuwes, 1992; 2010) and then becomes “top-down” attentional orientation (slower, effortful) which is a controlled process based on the cognitive characteristics of the observer and depending on the observer’s aims (Cooper & Langton, 2006; Itti & Koch, 2001; Yarbus, 1967). Emotional salience corresponds to the emotional charge, valence (positive, negative, and neutral) and intensity associated with every object in a visual scene (Bradley & Lang, 1994; Theeuwes, 2010; Landragin, 2011). When a face is present in a visual scene it is the most salient object (Flechsengar et al., 2018). Moreover, the facial movements consecutive to the facial expressions lead to a modification of the weight of emotional saliency of the different ROI (eye, nose, and mouth regions) intended to capture the observer’s gaze. Once the attention is guided on the salient parts of the face, the search for relevant emotional cues for the recognition of emotions begin under the aegis of “top-down” type attention orientation mechanisms. In AD there is impairment of both bottom-up and top-down mechanisms of attention orientation (Possin, 2010; Li et al., 2012) leading to disorganized search for facial emotional visual cues during FER (Polet et al., 2021,2022; Ogrocki et al., 2000; EYE-TAR (AD+) study). In bv-FTD, there is an impairment of top-down attentional orientation mechanism following prefrontal cortex lesions leading to a modification of the connectivity between the dorsal fronto-parietal network and the default mode network (Zhou et al., 2010; Day et al., 2013; Rytty et al., 2013). The orbitofrontal cortex, brain region of the prefrontal cortex, is a key region of salience network (Seeley et al., 2010; Day et al.,

2013) and social cognition (Garcia-Cordero et al., 2016; Baez et al., 2019). Furthermore, a lesion of the orbitofrontal cortex resulted in disinhibition (Mendez et al., 2008; Schroeter et al., 2011) and unorganized eye-gaze strategies during FER: increased number of fixations and a total loss of emotional salience with identical observation of faces, whether they express an emotion or not (Polet et al., 2022).

Considering this basis, we suggest that FER can be rehabilitated because this ability relies on many cognitive abilities and many brain regions suggesting that different compensatory mechanisms to the restoration of the function may be possible. Concerning the cognitive remediation of FER, we also suggest that it would be a remediation of visual attention consisting in automatizing the search for emotionally salient information on the face, mostly in the eye region.

But how does it work in patients with NDD despite their diffuse cognitive disorders and in particular their amnesic syndromes? This question is fundamental in this thesis work because many of the clinician or researcher colleagues argued during meetings or congresses that this cognitive remediation would not work within this population and that the possible benefits would only be present for a noticeably short time frame. They forgot that the TAR program relies on cognitive remediation techniques that have already shown their effectiveness in people with NDD, even with amnesic syndrome, such as shading, error-less learning and spaced retrieval. Shading consists of gradually reducing the assistance provided (Vallat-Azouvi & Le Bornec, 2013). Error-less learning organizes learning in such a way as to avoid the production of errors (Erkes et al., 2009). Spaced retrieval is based on increasing the time interval for recalling information until it is retained in long-term memory (Erkes et al., 2009). These implicit learning techniques, used together in people with NDD at mild to moderate stages, make it possible to durably automate several types of learning such as learning new semantic knowledge, new procedural skills, or new episodic information (Erkes et al., 2009; Vallat-

Azouvi & Le Bornec, 2013; Small & Cochrane, 2020). Our hypothesis was that these learning techniques would also sustainably improve FER ability by automating facial emotional information retrieval strategies, which our results support.

The FER-targeted remediation program enhanced the ability to recognize emotional cues on faces in an un-ecological setting with faces that have low emotional salience (static faces). Additionally, it helped to strengthen the skills for observing faces in motion (dynamic faces), which are emotionally more salient and easily draw attention. This last point suggests that the TAR program can also be applied to NDD patients at a mild stage, without FER impairment, to prevent the appearance of BPSD, the strategies for observing dynamic faces having deteriorated in the control group but not in the TAR group in the "EYE- TAR(AD+)" study.

Furthermore, we have seen that as FER performances were increasing, BPSD level were decreasing, confirming the link between impairment of FER and BPSD (Gregory et al., 2002; Ibañez & Manes, 2012; Kempnich et al., 2018; Polet et al., 2022; Santamaría-García et al., 2016; Torralva et al., 2009). Nevertheless, given the magnitude of the effect of TAR program on BPSD, and the fact that the last module of the TAR program consists of recognizing ambiguous facial expressions in complex social scenes, it is reasonable to think that TAR not only improved FER ability but has also improved other social cognition skills such as empathy and Theory of Mind.

Empathy is the ability to share and understand the emotional states of others (Decety & Lamm, 2006). It is close to the Theory of Mind, which designates the ability to infer mental states and understand them (Duval et al., 2011). The affective component of empathy consists in automatically simulating the feelings of others (Shamay-Tsoory et al., 2009), which is necessary for FER (Coricelli, 2005). The cognitive component of empathy and affective Theory of Mind are similar abilities (Dvash & Shamay-Tsoory, 2014) and correspond to other

perspective taking to attribute an emotion to them (Decety & Lamm, 2006). The cognitive Theory of Mind makes it possible to understand, infer or reason about the thoughts, beliefs, or intentions of others (Duval et al., 2011; Shamay-Tsoory, 2007). In AD, both affective and cognitive Theory of Mind are impaired due to prefrontal cortex lesions (Kalbe et al., 2010; Völlm et al., 2006; Shamay-Tsoory & Aharon-Peretz, 2007; Gregory et al., 2002).

Moreover, the literature demonstrated a link between an impairment of empathy and Theory of Mind and BPSD in AD (Fujino et al., 2014). The FER, empathy and Theory of Mind are very close abilities (Decety & Jackson, 2006; Dvash & Shamay-Tsoory, 2014), these abilities being correlated (Henry et al., 2006; Turner & Felisberti, 2017) and relying on similar brain regions (Hiser & Koenigs, 2018; Mier et al., 2010; Spunt & Adolphs, 2019). We have seen previously that these abilities are based on information from the eye region, but they are also based on the interpretation of the gaze direction, essential information for perspective taking (Samson et al., 2004; 2007; Duval et al., 2011; Achim et al., 2013). Gaze detection and interpretation of gaze direction are mechanisms dependent on attention orientation abilities, all these abilities being the basis of the shared attention system which intervenes in most social cognition skills (Stephenson et al., 2021) (See Fig.2).

As a result, we suggest that TAR would directly target FER and indirectly empathy and ToM due to improved shared attention ability, for a diffuse remediation of social cognition. To test this hypothesis, it would be necessary to add tests of empathy (such as the Empathy Quotient, Baron-Cohen & Wheelwright, 2004) and of Theory of Mind (such as the reading the mind in the eyes test, Baron-Cohen et al., (2001) or the faux pas test, Desgranges et al., (2012)) and also to measure the gaze strategies when observing complex visual social scenes, in which ambiguous facial emotions should be recognized. Moreover, it should be interesting to measure

the patient’s own facial expressions during FER to evaluate the “chameleon effect” (automatic mime of a facial expression) which is a marker of affective empathy (Wicker et al., 2003).

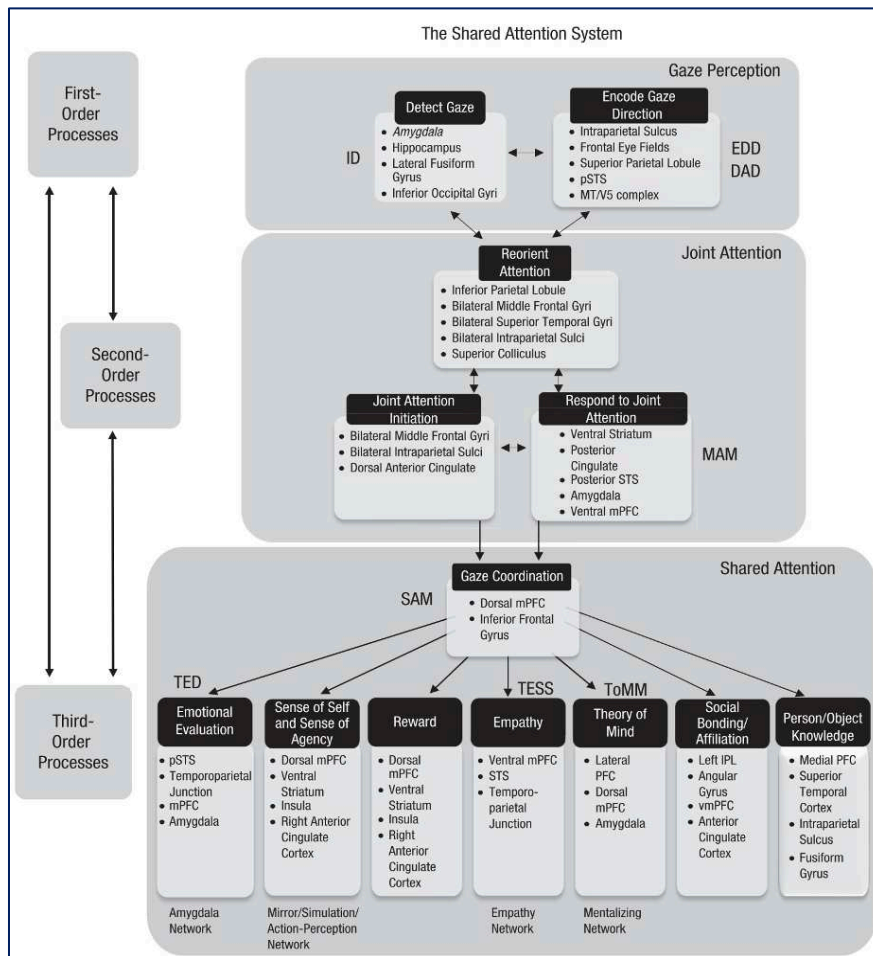


Fig.2. The shared-attention system (Sthephenson et al., 2021) *

All these findings reinforce the “triple link hypothesis” between social cognition, eye-gaze strategies and BPSD. These three components can be equated to three cognitive domains, namely social cognition, attention and executive functions, involving multiple common and strongly inter-connected brain networks (such as the default mode network, fronto-parietal control network and salience network) (Fig.3) (Lang et al., 2020 a,b; Matsuoka et al., 2021; Jin Yoon et al., 2021).

* This figure shows how first, second, and third order processes are involved in facilitating gaze detection, leading to the act of joint attention, which is a necessary precursor to shared attention when both agents are aware of each other’s attentional state, which can lead to important social cognitive outcomes: emotional evaluation, sense of self and agency, reward, empathy, theory of mind, social bonding/affiliation, and person knowledge. In this model, there is all of Baron-Cohen’s (1994, 2005) conceptualized mechanisms (ID, intentionality detector; EDD, eye-direction detector; SAM, shared-attention mechanism; TED, the emotion detector; TESS, the empathizing system; ToMM, theory-of-mind mechanism) and those of Perrett and Emery (1994; DAD, direction-of-attention detector; MAM, mutual-attention mechanism). There are, subserving brain regions for each of the processes in the model, and in addition, and the “social brain” networks highlighted by Stanley and Adolphs (2013) the amygdala, empathy, mentalizing, and mirror/simulation/action-perception networks. STS, superior temporal sulcus; IPL, inferior parietal lobule; PFC, prefrontal cortex; m, medial; p, posterior; vm, ventromedial.

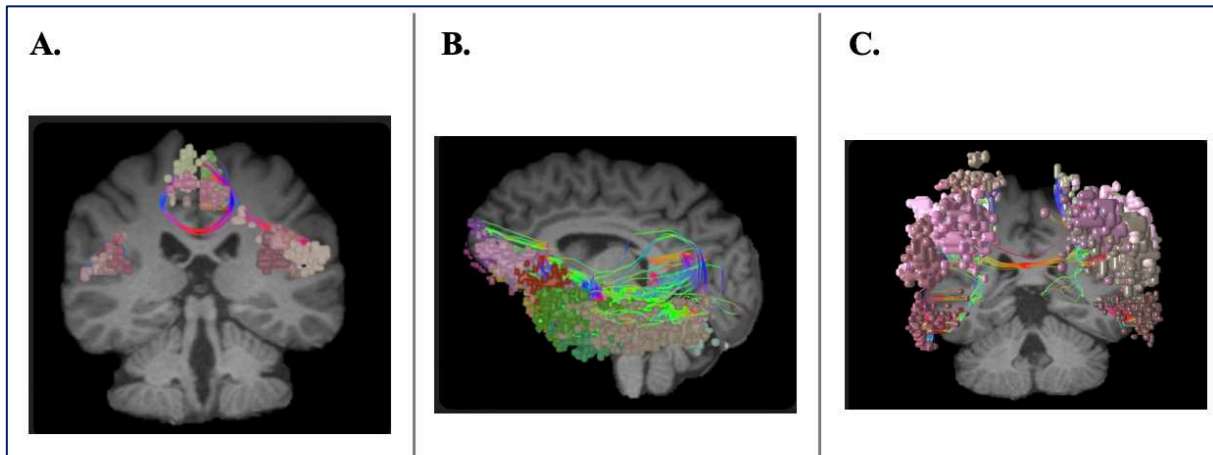


Fig. 3. Brain networks involved in the « social brain network » (<https://www.o8t.com/>, n.d)
A. Salience Network. **B.** Default Mode Network. **C.** Central Executive Network.

2.2. A better quality of life for the “patient/family caregiver” duo following the cognitive remediation of the FER ability?

The caregiver burden affects the physical, psychological, social relationship and quality of life of the caregiver (Srivastava et al., 2016). FER ability increasing in individuals with NDD might improve their communication skills (Kordsachia et al., 2017), and consequently the quality of the relationship between the patient and the caregiver (Carton et al., 1999; Kornreich et al., 2002; Hofer et al., 2009; Janssens et al., 2012; Kordsachia et al., 2017). At the same time, the decrease in the level of BPSD observed in our studies, has probably improved the family caregiver’s quality of life. Interestingly, in our study we observed a significant decrease for apathy which is the most frequent BPSD in AD (Zhao et al., 2016) and requires more support, management, and resource use (community health care services), when this BPSD is present, therefore resulting in high level of family caregiver burden (Cheng, 2017; De Vugt et al., 2006; Sherman et al., 2018). As a result of the decrease in the family’s caregiver’s stress level, it is likely that the latter has also improved their own FER (Martinez et al., 2018) and Theory of Mind abilities (Formica et al., 2020), and therefore their abilities to manage BPSD (Martinez et al., 2018; Formica et al., 2020).

Presence of BPSD can be decisive for placement decision in nursing home (Brodaty et al., 2004; Gilley et al., 2004; Porter et al., 2016; Rive et al., 2010; Vandepitte et al., 2018). Furthermore, together with the stage of the severity of dementia, they lead to an increase in healthcare costs (Rattinger et al., 2015; Wübker et al., 2015; Rattinger et al., 2019). Institutionalization entails a significant financial burden for families, estimated at on average €32,506.73 per year in Europe for dementia (Cantarero-Prieto et al., 2019) and \$94,637 in the United States for AD, that is a higher financial burden compared to other diseases (Kelley et al., 2015), increasing the level of caregiver burden and impacting their quality of life. Furthermore, it has been shown that delay institutionalisation of an individual with AD may increase the time spent with their loved ones and improve their quality of life and their life expectancy (McClendon et al., 2006) If, as we believe, improving the FER ability makes it possible to delay institutionalization, this would therefore reduce this major source of stress for the families of the patient.

Also, admission into a nursing home increases the probability of anxiety disorders, depression and other BPSD that may have a negative impact on general well-being and on, poorer physical health in the patient (Brodaty et al., 2001; Scocco et al., 2006) leading to a low quality of life (Leon-Satas et al., 2013). We suggest that a patient low level of quality of life related to institutionalization indirectly impacts the family's caregiver's level of quality of life.

BPSD are also associated with more long-term hospitalizations, misuse of medications and increased use of health care services (Altomari et al., 2022; Brodaty et al., 2014; Eikelboom et al., 2019; Hongisto et al., 2018; Isik et al., 2019). Often, productive BPSD require the use of pharmacological interventions in nursing home such as benzodiazepines, hypnotics, antipsychotics, or antidepressants (Iaboni et al., 2016; Ye et al., 2018). These medications have potential side effects, that may lead to cognitive impairment and to increase the risk of falls (The Society for Post-Acute and Long-Term Care Medicine, 2013; Woolcott et al., 2009).

Based on all these findings, lower BPSD would be associated to a higher quality of life for the patient/family caregiver duo, and therefore could delay institutionalization and decrease the use of psychotropic drugs. To confirm these hypothesis, quality of life scales could be used at baseline and at the end of a FER-targeted cognitive remediation program to assess the effect of this program on the quality of life. The change in scores on these scales could also be correlated to changes in FER, BPSD and caregiver burden scores.

2.3.Effects beyond the patient/caregiver settings?

Our results showed a decrease in BPSD after a FER-targeted cognitive remediation program. Consequently, this program could be generalized for all areas of neurological and psychiatric pathologies, wherein BPSD and social cognition disorders are extremely frequents (Bertoux, 2022).

Nonpharmacological interventions are preferred as first-line treatments for BPSD management (Ye et al., 2018; Qaseem et al., 2016) because they have no side effects unlike drugs (Oliveira et al., 2015). FER targeted programs can be done in groups and allow to stimulate social cognition abilities. As result, we believe that FER cognitive remediation program could be the most appropriate non-pharmacological intervention in NDD, since the non-specific non-pharmacological interventions such as schema therapy (Porter et al., 2016) or cognitive stimulation therapy (Garcia-Casal et al., 2017) did not affect the FER ability. A complementary study measuring the impact of the TAR program on the prescription of psychotropic drugs could be useful in this regard.

The beneficial effects of a FER targeted intervention by neurostimulation and pharmacological approach would also be beneficial, but this field must be studied further as the effects are not yet consensus.

As we have seen previously, acting on BPSD therefore means acting to keep the patient at home. Admission to the nursing home care for an individual with dementia constitutes an

economic burden not only for the family but also for the society as a whole. Regarding the World Health Organization, in Europe the cost of care for the estimated 14.1 million individuals with dementia amounted to €392 billion in 2019 (WHO, 2021). Furthermore, as seen previously, the institutionalization of an individual with AD entails a high societal cost, even more in the presence of productive BPSD, for example an estimated incremental cost of \$4,3 billion in the case of agitation (or \$50,588 per individual) in the United States (Cloutier et al., 2019). Moreover, the presence of BPSD leads to earlier institutionalization (Broadt et al., 2004; Gilley et al., 2004; Rive et al., 2010). Regarding these points, if our results are confirmed, the fact that acting on BPSD would have double benefits both for the family and for society by leading to cost-saving (Wübker et al., 2015). The latter will be more valuable for Western societies where the number of people with dementia will increase significantly in the context of the aging of the population, which could represent a major societal problem in the future.

3.LIMITATIONS

This thesis works do have several limitations. Firstly, one of our principal objectifs was to assess FER ability by a more ecological way than traditional manner (static FER assessment). That's why, we included ADFES test as dynamic FER assessment. Nevertheless, because this test is based only on the visual modality (with only the visible face), it neglects many factors influencing the FER, making it an unecological test. In real world scenarios, facial expressions are often accompanied by vocalizations, body, hand, head, and eye gestures, and their recognition can be influenced by other senses such as touch or smell (Keltner & Cordaro, 2017; Keltner et al., 2016; Scherer & Ellgring, 2007). The perception of expressions can be influenced by the direction of gaze and head, which can indicate where the person expressing the emotion is focusing their attention (Adams & Kleck, 2005; Hess et al., 2007; Milders et al., 2011; Rigato & Farroni, 2013). For example, when someone looks directly at you, it usually means they are approaching you and may be feeling happy or angry. On the other hand, if someone looks away

from you, it usually means they are avoiding you and may be feeling sad or scared (Fig. 4). When experiencing fear, the direction of a possible threat can be inferred from the head direction and gaze angle (Bindemann et al., 2008; Adams & Kleck, 2003; Sander et al., 2007). Based on these points, we suggest that a lack of cues, especially gaze cues, and head direction can explain the specific fear impairment in our AD patients. The ADFES test has already a condition with head direction, so further studies including multimodal FER test combining static and dynamic facial expressions with multiple conditions (i.e., averted gaze vs direct gaze for fear expression, etc) would be useful to assess FER ability accurately. Evaluating the FER ability is a crucial point as this ability is based on several sensory modalities and several different sources of information, so various ways of assessing this ability can lead to contradictory results. And, several compensation mechanisms may be possible in ecological conditions, explaining the significant heterogeneity of results observed in the literature regarding the FER ability in AD.

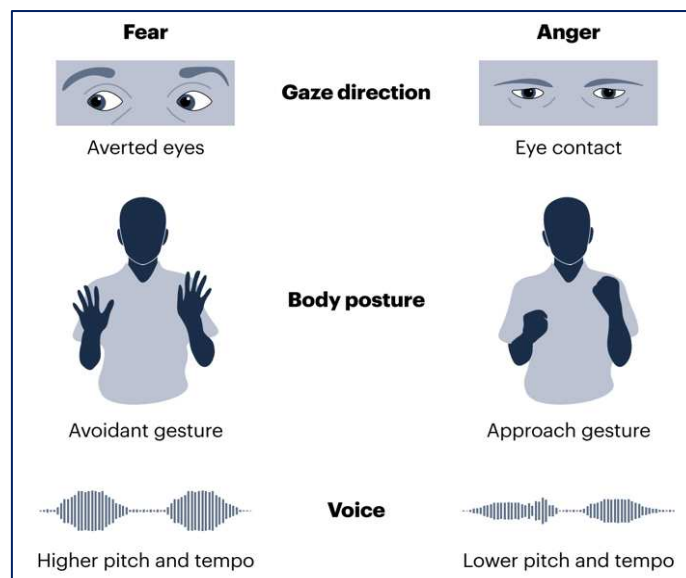


Fig. 4. Multiple channels of emotion recognition information (Krumhuber et al., 2023)

Secondly, although one of our main goals was to confirm our preliminary study's results with larger sample sizes, these samples remained modest in "EYE-TAR (AD+)". We faced difficulties in participants recruitment, mainly due to the availability constraints imposed by

our protocol: patients had to come on site for 1 hour, twice a week, for 6 weeks, then patient-caregiver couples had to be available for assessment's sessions (i.e., 3 appointments approximately 1 hour each). Additionally, some patients or family caregivers refused to participate because they did not understand the value of a program targeting the FER ability. Others have participated in the first sessions and then show reluctance, with a low level of motivation faced to this type of program. That's why, we think that the TAR program should be adapted to NDD, by adding some preliminary sessions to present the aims of this intervention to both patient and family caregivers that would increase the level of adherence.

Due to small samples sizes of our studies ("EYE – TAR (MA) Follow up" and "EYE-TAR (AD+)"), we had to adapt our statistical methodology with the use of nonparametric test, and we could not apply a correction for p values, for example correction of Bonferroni, as recommended by other authors (Bender & Lange, 1999; Perneger, 1998). In addition, we had to multiply the statistical analyzes increasing the alpha risk which constitutes a methodological bias. Nevertheless, for these reasons, our results must be confirmed with larger samples that would allow us to use more powerful parametric statistical tests.

Finally, the conclusions from our literature review and meta-analysis, we provide the scientific arguments that an improvement in the ability of FER in NDD could be possible. However, these conclusions are based on a limited number of studies, most of which had small sample sizes. Additionally, only the cognitive approach had FER improvement as a primary objective, while the other approaches had it as a secondary objective. Even so, although this limit, we believe that the works of this thesis would encourage further studies on this field.

4.PROSPECTS AND AVENUES

Following this thesis work, we argue that FER-targeted cognitive remediation effectively enhances FER abilities while reducing BPSD in individuals with NDD. In the following section, we will provide specific clinical applications for the management of individuals with NDD and

their caregivers. This work also proposes new avenues for further research to validate these findings on a larger scale and to improve effectiveness of this type of approach, as illustrated in Figure 5.

4.1. Prospects for clinical routine

As our results demonstrated the effectiveness of the cognitive remediation of FER recognition in AD, we propose applying this type of intervention in routine care as a non-pharmacological therapy for BPSD and to strengthen social abilities (as in schizophrenia for example).

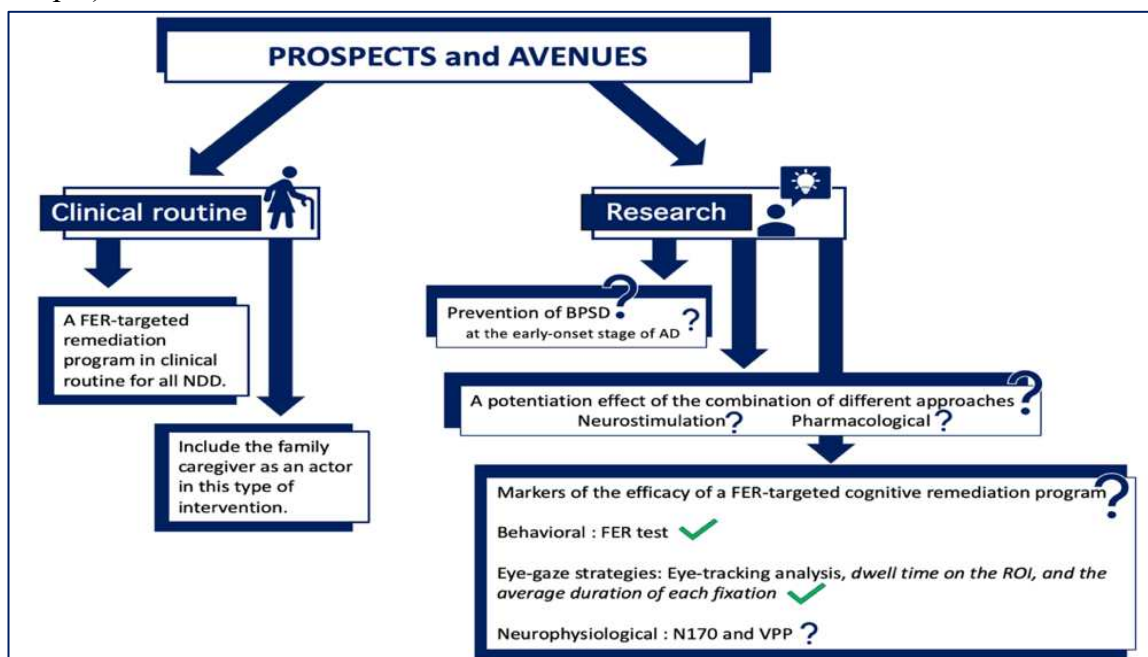


Fig. 5. Illustration of the thesis prospects and avenues. AD, Alzheimer's Disease; BPSD, Behavioral and Psychological Symptoms of Dementia; FER, Facial Emotion Recognition; NDD, Neurodegenerative Diseases; VPP, Vertex Positive Peak.

We also suggest extending this type of intervention to other NDD. Indeed, the FER targeted cognitive program was successful in HD (Kempnich et al., 2017), and BPSD are common in NDD frequently supported in memory clinics such as bv-FTD (Santamaria-Garcia et al., 2016; Ranasinghe et al., 2016), Lewy body dementia (Ballard et al., 1999) or PD (Weintraub et al., 2015). We believe this intervention could be more effective in bv-FTD

because BPSD are at the forefront of this disease. A study comparing the effectiveness of the TAR program according to the NDD would verify this hypothesis.

Based on two observations, our last proposal for clinical routine application consists in including the family caregiver as an active actor in this type of intervention. Firstly, family caregiver's own social cognition skills are impaired due to the stress of caring for a person with NDD (Formica et al., 2020; Martinez et al., 2018). We believe that a cognitive intervention such as TAR program would improve the family caregivers' social cognition abilities, allowing them to better understand their loved ones and therefore reducing their stress level. Secondly, family caregivers initially did not understand the usefulness of this type of intervention. After explaining the link between BPSD and social cognition, they gradually adhered to the program. A number of them asked to continue this type of intervention at the end of the study protocol. This convinced us that there would be a definite interest in coupling the TAR program sessions with psychoeducation sessions for family caregivers focused on BPSD and social cognition in NDD. This combination would provide the necessary training for the family caregivers, allowing them to shift from a role of passive actor to that of an active partner in managing their loved ones' BPSD. This can also help decrease the caregiver's stress and burden. A study including the family caregivers during TAR sessions therefore seems relevant to us.

4.2. Prospects for research

4.2.1. Preventive effect on BPSD?

In EYE-TAR (AD+) study, we included AD participants at a mild-moderate stage with significant BPSD, our objective being to highlight an effect of the TAR program on these BPSD. If participants had been recruited at an earlier stage, it would not have been possible to demonstrate this effect. As the effectiveness of this type of intervention on BPSD was demonstrated, with probable long-term effects, in particular a potential delay in

institutionalization, we wonder what would be the effects of this type of intervention on individuals at an early stage of AD? Two studies have been conducted in pre-symptomatic stage of HD by cognitive approach (Kempnich et al., 2017) and pre-symptomatic stage of FTD by neurostimulation approach (Benussi et al., 2020), both resulting in FER improvement, thus indicating an effectiveness of interventions even in pre-clinical stages of NDD. We hypothesize that this type of intervention could strengthen the social cognition abilities of people with NDD and therefore could delay the onset of problematic BPSD for family caregivers and could allow a more significant delay in the institutionalization of these patients. In this context, the TAR program would no longer be used as a FER remediation tool but would rather be used as a tool for preventing BPSD onset. A study including NDD patients at an early stage could confirm this hypothesis. Particular attention would be paid to patients with bv-FTD and other "frontal" dementias, social cognition disorders and BPSD being inaugural there (Duclos et al., 2015).

4.2.2. A potentiating effect of the combination of different FER targeted approaches?

Our meta-analysis concluded that three different approaches, namely cognitive remediation, neurostimulation, and pharmacological intervention, can improve FER ability in NDD. However, no study has yet investigated the combined effect of these interventions. Given our positive findings, it would be worthwhile to explore a combination of these approaches to highlight the potential effect on FER ability.

The combination of cognitive remediation / neurostimulation approaches could be beneficial. We believe that firstly, because combining these approaches is practical since non-invasive neurostimulation techniques do not produce any side effects (they are considered marginal for non-invasive neurostimulation Yavari et al., (2018)). Secondly, significant improvement in FER performances was obtained with tDCS after 2 weeks of left prefrontal cortex stimulation in individuals with bv-FTD (Benussi et al., 2020). To investigate such combination, we need to analyze how tDCS impacts FER abilities in other NDD. Then, we

could compare those results with the outcomes of combining tDCS with a cognitive FER-targeted intervention.

Combining the cognitive approach with TMS, would be a promising method for further exploration. Indeed, compared to tDCS, TMS has shown superior efficacy in improving cognitive abilities and BPSD in AD (Elder et al., 2019; Grady et al., 2001; Murphy et al., 2023; Suemoto et al., 2014; Turriziani et al., 2012), and allows to stimulate brain areas more precisely and deeply (Pascual-Leone, 2000). This technique is commonly used in various neurological and psychiatric disorders (Burt et al., 2002; Fregni & Pascual-Leone, 2007; Hallett, 2007). In AD, cognitive functioning significantly improves when cognitive training is combined with rTMS whether patients were medicated (Bentwich et al., 2011) or not (Sabbagh et al., 2020). As far as we are aware, no research has been carried out using TMS to improve FER ability in individuals with NDD. However, TMS has been shown to offer clinical benefits and improvements in FER in cases of depression (Berlim et al., 2012). After considering all these observations, it appears reasonable to use TMS for improving FER, in combination with a FER-targeted cognitive remediation program, to optimize FER ability improvement in NDD.

As the TMS can reach distant areas functionally connected to the stimulated region, this technique permits the stimulation of the amygdala (and more generally the amygdala network) via the stimulation of the orbitofrontal cortex which is connected by the uncinate fasciculus (Liu et al., 2013; Wang & Olson, 2018), or via the stimulation of the STS (superior temporal sulcus) also connected to the amygdala (Pitcher et al., 2017), all of these brain structures are key brain structures for social cognition (Wang & Olson, 2018). The amygdala constitutes a hub between the main networks involved in social cognition such as the salience network, the default cerebral network, mirroring network, mentalizing network, face network, dorsal attentional network... (Christidi et al., 2018; Wang & Olson, 2018), and it is involved in recognition of all facial expressions (Morris et al., 1996; Whalen et al., 1998; Hoffman et al.,

2007), in gaze detection (Gamer et al., 2013; Stephenson et al., 2021) and in directing attention (Adolphs & Spezio, 2006). Furthermore, stimulation of the orbitofrontal cortex and STS would also be appropriate, as the orbitofrontal cortex is also a key brain structure of FER ability (Hornak et al., 1996; 2003) and is involved in behavioral control (Mendez et al., 2006; Schroeter et al., 2011), and the STS is involved in Theory of Mind and in the processing of gaze direction (Stephenson et al., 2021). In addition, a study has shown that STS stimulation by TMS resulted in modification of attention orientation toward the eye region in healthy subjects (Saitovitch et al., 2016). For these reasons, we believe that the cognitive remediation / TMS coupling would potentiate their effectiveness on FER performance by acting more effectively on the networks governing gaze strategies during FER.

A combination of pharmacological and cognitive approaches may also be interesting to investigate in future research. As we only found a beneficial effect of SSRI on FER ability, a possible combination could be carried out using SSRI or ketamine infusion since it increased DMN and SN connectivity (Evans et al., 2018). We suggest that the later can be a new avenue to investigate to improve FER abilities in NDD.

Finally, further studies could be carried out to determine the effects of combined approaches (cognitive-neurostimulation vs. cognitive-pharmacological vs. pharmacological-neurostimulation approaches). See to compare these results with triple approaches combination. In addition, cross-over designed protocols would be interesting to clarify the order of the approaches to apply.

4.2.3. Towards finer and more relevant effectiveness markers?

Based on our studies, we recommend establishing several finer and more relevant markers of the effectiveness of the intervention. Ideally the FER-targeted intervention program should be based on a multi-baseline evaluation protocol integrating a primary efficacy marker and several secondary efficacy markers:

- **primary efficacy marker** would consist of the variation in the FER ability performances assessed in an exhaustive and more ecological manner (see limitations section), i.e., with static and dynamic materials, integrating gaze direction, body posture, prosody and social context.
- **secondary efficacy markers** would consist of behavioral and physiological changes indicating a learning effect following the FER-targeted intervention. As behavioral marker, we recommend using eye-tracking technology to highlight changes in eye-gaze behaviors following FER-targeted intervention, and more specifically measurement of the dwell time in the eye region and the average fixation duration. These are respectively markers of information search of the bottom-up type and of the top-down type. As physiological marker, the recording of event-related potentials such as VPP and N170 seems interesting, because a modification of these markers following FER-targeted intervention could indicate an improvement in the processing of the emotional salience of faces (Luo et al., 2010).



CONCLUSION

This thesis works demonstrated that the FER ability can be enhanced in NDD, with sustainable beneficial effects despite the evolutionary of these diseases.

More precisely, the cognitive approach seems to be the most effective, followed by neurostimulation and pharmacological approaches to improve FER ability in NDD. Then, we showed that a FER targeted cognitive remediation program improved the FER ability. This improvement was associated with a modification of eye-gaze strategies while scanning expressive faces. The latter could be a result of acting on the “bottom-up” and “top-down” attentional orientation networks allowing a better attention orientation to the emotionally salient areas of the face. In addition, the improvement has resulted in a decreased of BPSD followed by a decrease in the level of family caregiver burden. These beneficial effects were maintained at one-month post intervention.

In the long term (> 2 years) we observed that short term beneficial effects were not sustained. However, we observed that all participants of the group that received a FER-targeted cognitive stimulation program continued to live in their homes, while all other participants were institutionalized due to behavioral disorders. We suggest that reduced BPSD might delay the entrance in institution, that should be confirmed by a larger sample.

This thesis suggests a new approach that would be now applied in therapeutic use for BPSD in the clinical routine for the patients with NDD. We highly encourage further studies to combine cognitive and neurostimulation approach to increase the effectiveness and sustainability of the interventions for the improvement of FER ability in all NDD. In addition, we highly recommend studying the effects of these approaches in early stage (pre-clinical stage?) of NDD to prevent BPSD and caregiver burden.



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APPENDIX

1. Preliminary study (Polet et al., 2021)

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DONNÉES FONDAMENTALES

Remédiation de la reconnaissance des émotions faciales dans la maladie d'Alzheimer et effets sur les stratégies d'observation, les troubles du comportement et le fardeau de l'aidant



Rehabilitation of facial emotion recognition in Alzheimer's disease and effects on observational strategy, behavioral disorders and family caregiver burden

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MOTS CLÉS

Maladie d'Alzheimer ;
Reconnaissance des
émotions faciales ;
Eye-tracking ;
Troubles du
comportement ;
Fardeau de l'aidant

Résumé

Introduction. — La reconnaissance des émotions faciales (REF) est altérée dans la maladie d'Alzheimer (MA) et est liée à un balayage visuel atypique. Cela engendre des troubles du comportement (TDC) et une majoration du fardeau des aidants.

Objectifs. — Mesurer l'effet d'une remédiation de la REF et l'impact sur les stratégies d'observation, les TDC et le fardeau des aidants.

Méthode. — Huit sujets MA ont été répartis en deux groupes : remédiation de la REF vs stimulation cognitive. La REF, les TDC, les mouvements oculaires et le fardeau de l'aidant ont été mesurés avant, après et 1 mois post-prise en charge.

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Résultats. – Il a été observé une amélioration de 11 % des performances de REF (avec augmentation significative pour la peur et la tristesse) dans le groupe remédiation et une baisse de 2 % dans le groupe contrôle. Ces résultats étaient liés à une modification des stratégies d'observation, une diminution des TDC et du fardeau de l'aidant avec maintien des effets dans le temps.

Conclusion. – La remédiation de la REF est une prise en charge envisageable dans la MA pour améliorer la qualité de vie patient/aidant.

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KEYWORDS

Alzheimer's disease;
Facial emotion
recognition;
Eye-tracking;
Behavioral disorders;
Family caregiver
burden

Summary

Background. – Facial emotion recognition (FER) is impaired in Alzheimer's disease (AD) and is linked to atypical visual scanning. This causes behavioral disorders (BD) and an increased family caregiver burden.

Objectives. – To measure the effects of FER rehabilitation and the impact on visual scanning, BD and caregiver burden.

Methods. – Eight AD subjects were divided into two groups: FER rehabilitation vs cognitive stimulation. FER, BD, eye movements and caregiver burden were assessed before, after, and one month post-treatment.

Results. – There was an 11% improvement in REF performances (with a significant increase for fear and sadness) in the rehabilitation group and a 2% decrease in the control group. These results were linked to alterations in visual scanning patterns, a decrease in BD and caregiver burden, with maintenance of these effects.

Conclusion. – This new approach in AD can be considered in order to improve patient and caregiver quality of life.

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La reconnaissance des émotions faciales (REF) est altérée dans la maladie d'Alzheimer (MA), avec des difficultés de reconnaissance des émotions négatives [1,2]. La REF, fondamentale dans les relations sociales, est également touchée dans des maladies comme la schizophrénie [3].

Ce déficit est associé à un balayage visuel atypique avec diminution du nombre de fixations sur les zones-clés du visage (yeux, nez, bouche) [4]. Dans la MA, les yeux sont moins observés [5,6].

L'altération de la REF entraîne une perturbation des relations interpersonnelles avec inadéquation des comportements sociaux et des capacités de communication, favorisant une diminution de la qualité de vie [7–9]. Des études montrent un lien entre déficit de REF et troubles du comportement (TDC) dans la MA [10–12]. Il existerait une triple interaction entre stratégies atypiques d'observation des visages émotionnels, déficit de REF et TDC [6].

Les TDC sont fréquents dans la MA [13], constituant le facteur principal d'épuisement de l'aidant familial [14]. Le trouble de REF est aussi associé à un fardeau et à un niveau de dépression accrus de l'aidant [15].

Dans ce contexte, la remédiation de la REF suscite un intérêt croissant. Développée pour des patients schizophrènes, le « training of affect recognition program » (TAR) a montré des résultats positifs sur la REF [16]. Le TAR a récemment été utilisé dans la MA montrant une amélioration globale la REF (en particulier surprise, dégoût

et expression neutre), avec un maintien des performances post-remédiation [17]. Une autre étude a démontré que la reconnaissance de la peur peut être améliorée dans la MA lorsque l'attention est orientée sur les yeux [18]. Ces études démontrent que la REF peut être améliorée dans la MA en lien avec une modification des stratégies d'observation.

Les objectifs de l'étude sont de confirmer que la REF peut être améliorée dans la MA en utilisant le TAR, montrer que cette amélioration est liée à une modification des stratégies d'observation et mettre en évidence une diminution conjointe des TDC et du fardeau de l'aidant. Pour cela, les performances de REF, TDC et le fardeau de l'aidant d'un groupe de personnes atteintes de MA seront évalués avant, après et un mois post-remédiation de la REF par le programme TAR, et seront comparés à un groupe de personnes atteintes de MA ayant bénéficié d'un programme classique de stimulation cognitive.

Méthodes

Participants

Recrutement parmi les patients suivis au centre mémoire du centre hospitalier Princesse-Grâce de Monaco (CHPG), de mars 2019 à janvier 2020. Critères d'inclusion : diagnostic de MA selon l'IWG-2 [19], MMS-E [20] ≥ 15 , sujet

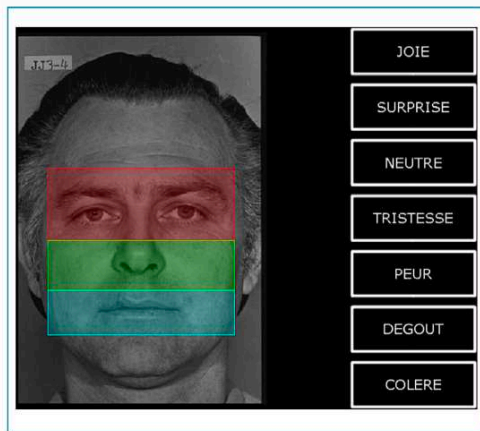


Figure 1. Visage « neutre », avec représentation des trois régions d'intérêt : les yeux en rouge, le nez en vert et la bouche en bleu.

accompagné d'un aidant familial et dont la participation à un atelier de stimulation cognitive était préconisée. Critères d'exclusion : anesthésie générale dans les trois mois précédant l'étude, trouble ophtalmologique ou neurologique empêchant la réalisation d'un examen d'*eye-tracking* ou de troubles neuropsychiatriques antérieurs au diagnostic de MA.

Huit participants recrutés et distribués aléatoirement en deux groupes : MA-TAR et MA-Contrôle. Les participants ont reçu une description détaillée des modalités de l'étude et signé un consentement éclairé.

Mesures

Fonctionnement cognitif

Mesuré avec le MMS-E [20].

Reconnaissance des émotions faciales (REF)

Évaluation de la reconnaissance des émotions de colère, dégoût, peur, tristesse, joie, surprise et expression neutre grâce à 28 photographies de visages issues de la batterie des visages d'Ekman [21] (4 photos/émotion, score total/28).

Les photos (noir et blanc, 22,2 × 14,7 cm) apparaissaient sur un écran (22 pouces, résolution 1920 × 1080 pixels, taux de rafraîchissement 60 Hz, luminance 250 cd/m², rapport de contraste statique 1000/1) avec un temps d'affichage maximum de huit secondes/photo. Le participant devait reconnaître l'émotion exprimée parmi les sept propositions (Fig. 1) et pointer sa réponse sur l'écran. Entre chaque photo, il devait fixer un point central.

Stratégies de regard durant la REF

Les stratégies de regard ont été étudiées à l'aide d'un *eye-tracker* (Mobile EyeBrainT2®, SURICOG). Deux caméras infrarouges filmaient les mouvements des yeux à une fréquence de 300 Hz (précision 0,25° à 60 cm de l'écran).

Une calibration initiale était réalisée (fixation de treize points consécutifs). Puis, pour chaque photo, le nombre et les durées des fixations ont été mesurés, ainsi que les durées d'exploration (en ms) sur quatre régions d'intérêt : visage entier, yeux, nez et bouche (Fig. 1). Une fixation était comptabilisée dès que les yeux restaient au moins 100 ms dans une zone de 1° × 1°.

Troubles du comportement (TDC)

Les TDC ont été mesurés avec le Neuropsychiatric Inventory (NPI) [22], échelle de 12 items correspondant à dix troubles psychocomportementaux (idées délirantes, hallucinations, agitation, dépression, anxiété, euphorie, apathie, désinhibition, irritabilité et comportements moteurs aberrants) et deux symptômes neurovégétatifs (troubles du sommeil et de l'appétit). Complété avec l'aidant familial, il permet d'obtenir un score sur 12 pour chaque TDC et un score total sur 144.

Fardeau de l'aidant

La pénibilité ressentie par l'aidant (fardeau) a été mesurée avec l'échelle de Zarit [23], composée de 22 questions sur la charge physique, émotionnelle et financière ressentie. Le score est sur 88.

Procédures

Design de l'étude

Chaque groupe bénéficiait d'une prise en charge de deux séances/semaine, durant six semaines, en suivant soit le programme TAR, soit un programme de stimulation cognitive (Fig. 2).

Pour chaque participant, trois évaluations ont été réalisées à T0, T1 et T2 (c'est-à-dire avant, à la fin et un mois post-programme). À chaque évaluation, l'efficacité cognitive globale et la REF (avec enregistrement des mouvements oculaires) ont été mesurées et les aidants complétaient le Zarit et le NPI. Notons qu'en raison de la pandémie de la COVID-19, l'évaluation T2 du groupe MA-Contrôle n'a pas pu avoir lieu.

L'étude suivait le principe des lignes de bases multiples. Pour le groupe MA-TAR, un effet spécifique et bénéfique du TAR était attendu sur les performances de REF. Le MMS-E servait d'indicateur neutre, aucun effet du programme TAR n'était prévu. Pour le groupe MA-Contrôle, aucun effet du programme de stimulation cognitive n'était attendu sur les différents indicateurs (MMS-E et REF).

Le protocole a reçu un avis favorable du Comité de pilotage de la recherche du CHPG et a été conduit conformément aux directives de la conférence internationale sur l'harmonisation pour les bonnes pratiques cliniques.

Training of affect recognition (TAR)

Ce programme comprend trois modules de quatre séances (en groupe, 1 h/séance, 2 séances/semaine), soit douze séances en tout. Module 1 : entraînement à identifier et discriminer les signaux faciaux prototypiques des six émotions primaires. Module 2 : favoriser un traitement holistique des visages émotionnels, une reconnaissance plus rapide et la distinction d'expressions de faible intensité. Module

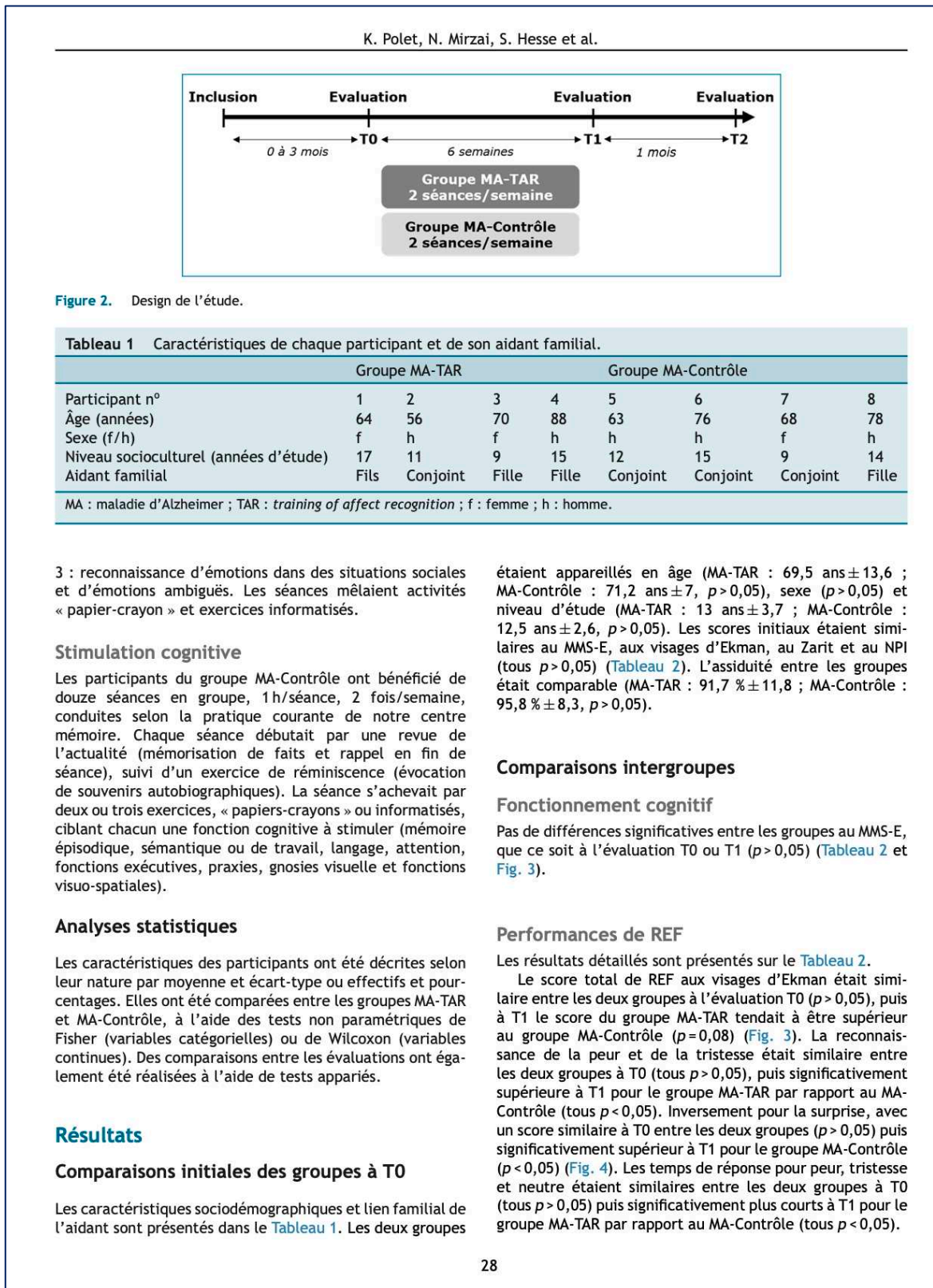


Tableau 2 Comparaisons des performances cognitives, de REF, des TDC et du fardeau de l'aidant entre les deux groupes, avant et post-programme.

	Évaluations à T0				Évaluations à T1			
	Groupe MA-TAR (n=4)		Groupe MA-Contrôle (n=4)		Groupe MA-TAR (n=4)		Groupe MA-Contrôle (n=4)	
		p-value		p-value		p-value		p-value
Score MMS-E (σ)	19,8 (2,9)	ns	19,8 (1,7)	ns	20,8 (3)	ns	19 (1,6)	ns
Score Visages Ekman (σ)	21 (2,9)	ns	16,2 (5,4)	ns	23,2 (3)	ns	16 (5,7)	0,08
Temps réponse Visages Ekman (σ)	4s (0,4)	<0,05	5,4s (0,8)	<0,05	3,8s (0,6)	<0,05	5,8s (0,4)	<0,05
Score Joie (σ)	3,8 (0,5)	ns	4 (0)	ns	4 (0)	ns	3,5 (1)	ns
Temps réponse Joie (σ)	2,3s (1)	ns	4,7s (1,2)	ns	5s (0,4)	ns	4,7s (1,4)	ns
Score Peur (σ)	2 (1,8)	ns	1 (1,2)	ns	3,2 (1)	ns	1 (0,8)	<0,05
Temps réponse Peur (σ)	4s (1,2)	ns	4,3s (0,6)	ns	3,2s (1)	ns	5,6s (0,7)	<0,05
Score Colère (σ)	3,5 (0,6)	ns	2,5 (1,9)	ns	3,2 (1)	ns	2,5 (1,3)	ns
Temps réponse Colère (σ)	4s (0,3)	<0,05	6,7s (1,2)	<0,05	4,1s (1,4)	<0,05	6,2s (0,5)	<0,05
Score Tristesse (σ)	1,5 (1,3)	ns	1,2 (1)	ns	3,5 (0,6)	ns	1,5 (1,3)	<0,05
Temps réponse Tristesse (σ)	6s (0,8)	ns	5,3s (0,6)	ns	4,1s (0,5)	ns	6,3s (0,7)	<0,05
Score Dégoût (σ)	3,8 (0,5)	ns	2,5 (1,3)	ns	3,2 (1,5)	ns	1,8 (1,3)	ns
Temps réponse Dégoût (σ)	3,7s (1)	<0,05	6,3s (1,1)	<0,05	2,7s (0,9)	<0,05	6,5s (0,5)	<0,05
Score Surprise (σ)	3,2 (1)	ns	2,2 (1)	ns	2,2 (0,5)	ns	3,5 (0,6)	<0,05
Temps réponse Surprise (σ)	3,5s (0,3)	ns	4,9s (1,7)	ns	4,3s (1,7)	ns	4,8s (1,3)	ns
Score Neutre (σ)	3,2 (0,5)	ns	2,8 (1)	ns	3,8 (0,5)	ns	2,2 (1,3)	ns
Temps réponse Neutre (σ)	4,8s (1,1)	ns	5,4s (1,2)	ns	2,8s (0,4)	ns	6,3s (0,8)	<0,05
Score NPI Total (σ)	22,8 (7,1)	ns	25,8 (13,8)	ns	10,8 (3,4)	ns	27 (17,4)	ns
Score idées délirantes (σ)	0,5 (1)	ns	2 (2,3)	ns	0,5 (1)	ns	3 (2,6)	ns
Score Hallucination (σ)	0 (0)	ns	0 (0)	ns	0 (0)	ns	0 (0)	ns
Score Agitation (σ)	1,8 (2,9)	ns	3 (2,6)	ns	0 (0)	ns	2,5 (3)	ns
Score Dépression (σ)	2,5 (3)	ns	3 (2,6)	ns	0,5 (0,6)	ns	2 (1,6)	ns
Score Anxiété (σ)	2,8 (3,6)	ns	5 (2)	ns	2,5 (2,6)	ns	4,8 (2,5)	ns
Score Euphorie (σ)	0 (0)	ns	0,5 (1)	ns	0 (0)	ns	1 (1,2)	ns
Score Apathie (σ)	8 (0)	ns	5,8 (3,3)	ns	3 (1,2)	ns	5 (3,8)	ns
Score Désinhibition (σ)	1,2 (1)	ns	0 (0)	ns	0,5 (1)	ns	0,2 (0,5)	ns
Score Irritabilité (σ)	2 (1,2)	ns	3,8 (1,7)	ns	1,2 (1,9)	ns	2 (2,7)	ns
Score Comport. Mot. (σ)	1,2 (1,9)	ns	1,8 (2,1)	ns	0,5 (1)	ns	3 (3,8)	ns
Score Sommeil (σ)	0 (0)	ns	0,2 (0,5)	ns	0,8 (1)	ns	0,2 (0,5)	ns
Score Appétit (σ)	3 (3,5)	ns	0,8 (1)	ns	1,2 (1,5)	ns	3,2 (2,5)	ns
Score Zarit (σ)	41 (5,3)	ns	25,2 (16,9)	ns	28,5 (7,2)	ns	29,8 (16,5)	ns

MA : maladie d'Alzheimer ; TAR : training of affect recognition ; MMS-E : Mini Mental State Examination ; NPI : Neuropsychiatric Inventory ; ns : non significatif (p > 0,05).

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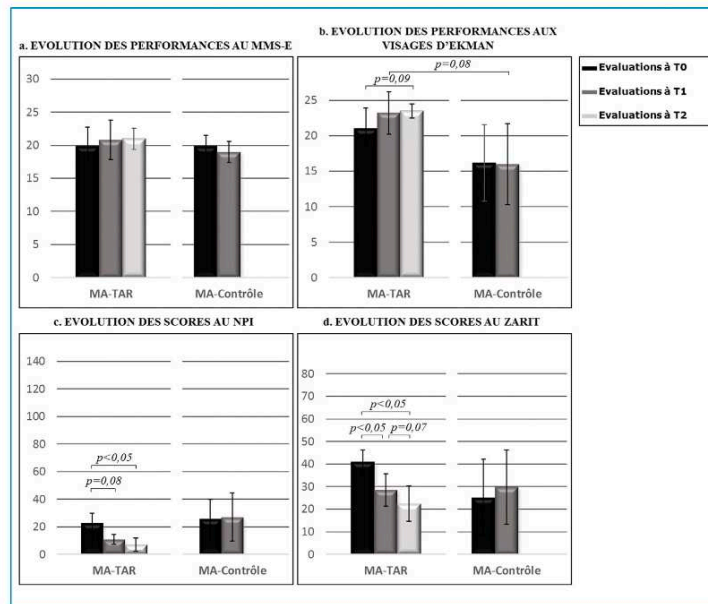


Figure 3. Comparisons des scores MMS-E (a), des scores totaux des visages d'Ekman (b), des scores NPI (c) et des scores Zarit (d) aux évaluations T0, T1 et T2. MA : maladie d'Alzheimer ; TAR : *training of affect recognition* ; MMS-E : Mini Mental State-Examination ; NPI : Neuropsychiatric Inventory.

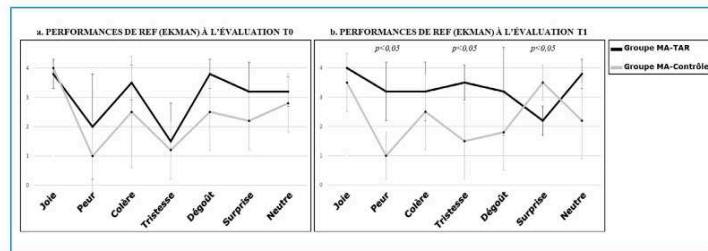


Figure 4. Comparaison des scores de REF entre les deux groupes avant et post-programme. REF : reconnaissance des émotions faciales ; MA : maladie d'Alzheimer ; TAR : *training of affect recognition*.

Stratégies de regard durant la REF

Les résultats significatifs sont présentés sur le [Tableau 3](#). Les deux groupes se distinguaient à T0 pour l'observation des visages de joie (les participants du groupe MA-TAR observaient davantage les yeux alors que ceux du MA-Contrôle observaient davantage le nez, tous $p < 0,05$) et de dégoût (temps moyen d'une fixation sur le nez supérieur pour le groupe MA-TAR, $p < 0,05$). Ces différences ne se retrouvaient plus à T1 ($p > 0,05$). Les autres résultats mettaient en évidence des modifications des stratégies d'observation post-programme avec apparition de différences significatives à T1. Ainsi, le groupe MA-TAR observait davantage les yeux (durée moyenne d'une fixation, % d'observation ou nombre de fixations, tous $p < 0,05$) pour la reconnaissance de toutes les émotions excepté la joie, et avait une

augmentation de la durée moyenne de fixation du nez pour la colère ($p < 0,05$) en comparaison du groupe MA-Contrôle.

Troubles du comportement et fardeau de l'aidant

Les résultats détaillés sont présentés sur le [Tableau 2](#). Pas de différence significative entre les 2 groupes aux scores du NPI et à l'échelle de Zarit à T0 et T1 (tous $p > 0,05$) ([Fig. 3](#)).

Comparaisons intra-groupes

Les résultats détaillés sont présentés sur les [Tableaux 4 et 5](#).

Tableau 3 Différences significatives des stratégies de regard (nombre et durées des fixations) observées entre les deux groupes avant et post-programme.

	Évaluations à T0			Évaluations à T1		
	Groupe MA-TAR (n=4)	Groupe MA-Contrôle (n=4)	p-value	Groupe MA-TAR (n=4)	Groupe MA-Contrôle (n=4)	p-value
Joie						
% d'observation RI yeux (σ)	61,2 (13,6)	18,8 (1,3)	<0,05	34 (24)	35,2 (23,2)	ns
% d'observation RI nez (σ)	14,2 (13,2)	61,5 (15,6)	<0,05	46,8 (17,5)	33,5 (13,5)	ns
Peur						
Temps moyen d'une fixation sur le visage (σ)	244 ms (52)	223 ms (37)	ns	292 ms (18)	214 ms (30)	<0,05
Temps moyen d'une fixation RI yeux (σ)	246 ms (47)	215 ms (50)	ns	287 ms (26)	231 ms (36)	0,05
Colère						
Nombre de fixations RI yeux (σ)	2,7 (0,7)	4,2 (5,5)	ns	4,9 (1,3)	2,3 (1,2)	0,05
% d'observation RI yeux (σ)	50,8 (6,2)	34,8 (29,9)	ns	58 (8)	33,5 (19,3)	0,05
Temps moyen d'une fixation RI yeux (σ)	253 ms (21)	200 (63)	ns	311 ms (39)	229 ms (51)	0,05
Temps d'observation RI yeux (σ)	652 ms (103)	1185 ms (1862)	ns	1478 ms (384)	528 ms (305)	<0,05
Temps moyen d'une fixation RI nez (σ)	247 ms (48)	237 ms (35)	ns	324 ms (61)	216 ms (48)	<0,05
Tristesse						
Temps moyen d'une fixation sur le visage (σ)	246 ms (19)	261 ms (95)	ns	300 ms (25)	239 ms (36)	<0,05
Temps moyen d'une fixation RI yeux (σ)	241 ms (42)	249 ms (102)	ns	322 ms (39)	210 ms (48)	<0,05
Dégoût						
Temps moyen d'une fixation RI yeux (σ)	282 ms (36)	218 ms (40)	ns	308 ms (51)	211 ms (42)	0,05
Temps moyen d'une fixation RI nez (σ)	260 ms (8)	209 ms (15)	<0,05	291 ms (22)	239 ms (72)	ns
Surprise						
Temps moyen d'une fixation sur le visage (σ)	256 ms (21)	252 ms (40)	ns	311 ms (35)	214 ms (41)	<0,05
Temps moyen d'une fixation RI yeux (σ)	264 ms (29)	220 ms (74)	ns	326 ms (51)	218 ms (51)	0,05
Temps d'observation RI yeux (σ)	686 ms (309)	1071 ms (1494)	ns	1340 ms (441)	632 ms (423)	0,05
Neutre						
Temps moyen d'une fixation RI yeux (σ)	269 ms (40)	235 ms (107)	ns	345 ms (66)	223 ms (23)	<0,05

RI : région d'intérêt ; MA : maladie d'Alzheimer ; TAR : training of affect recognition ; ns : non significatif (p > 0.05).

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Tableau 4 Évolution des performances au MMS-E, de REF et évolution des scores au NPI et au Zarit du groupe MA-TAR, avant, post et un mois post-programme.

	Groupe MA-TAR (n = 4)			
	T0	T1	T2	
Score MMS-E (σ)	19,8 (2,9)	20,8 (3)	21 (1,6)	ns
Score Visages Ekman (σ)	21 (2,9)	23,2 (3)	23,5 (1)	ns
Temps réponse Visages Ekman (σ)	4s (0,4)	3,8s (0,6)	3,1s (0,4)	ns
Score Joie (σ)	3,8 (0,5)	4 (0)	3,8 (0,5)	ns
Temps réponse Joie (σ)	2,3s (1)	5s (0,4)	3,7s (2,5)	<0,01
Score Peur (σ)	2 (1,8)	3,2 (1)	2 (0,8)	ns
Temps réponse Peur (σ)	4s (1,2)	3,2s (1)	3s (0,4)	ns
Score Colère (σ)	3,5 (0,6)	3,2 (1)	3,2 (1)	ns
Temps réponse Colère (σ)	4s (0,3)	4,1s (1,4)	3,1s (0,7)	ns
Score Tristesse (σ)	1,5 (1,3)	3,5 (0,6)	3,5 (0,6)	0,09
Temps réponse Tristesse (σ)	6s (0,8)	4,1s (0,5)	3s (0,7)	<0,01
Score Dégoût (σ)	3,8 (0,5)	3,2 (1,5)	3,8 (0,5)	ns
Temps réponse Dégoût (σ)	3,7s (1)	2,7s (0,9)	2,9s (0,5)	<0,01
Score Surprise (σ)	3,2 (1)	2,2 (0,5)	3,2 (1)	ns
Temps réponse Surprise (σ)	3,5s (0,3)	4,3s (1,7)	3,7s (1,2)	ns
Score Neutre (σ)	3,2 (0,5)	3,8 (0,5)	4 (0)	ns
Temps réponse Neutre (σ)	4,8s (1,1)	2,8s (0,4)	2,7s (0,8)	0,08
Score NPI Total (σ)	22,8 (7,1)	10,8 (3,4)	7 (4,8)	0,08
Score Idées délirantes (σ)	0,5 (1)	0,5 (1)	0,2 (0,5)	ns
Score Hallucination (σ)	0 (0)	0 (0)	0 (0)	ns
Score Agitation (σ)	1,8 (2,9)	0 (0)	0,2 (0,5)	ns
Score Dépression (σ)	2,5 (3)	0,5 (0,6)	0,2 (0,5)	ns
Score Anxiété (σ)	2,8 (3,6)	2,5 (2,6)	0,2 (0,5)	ns
Score Euphorie (σ)	0 (0)	0 (0)	0,5 (1)	ns
Score Apathie (σ)	8 (0)	3 (1,2)	2 (0,8)	0,09
Score Désinhibition (σ)	1,2 (1)	0,5 (1)	0,5 (1)	ns
Score Irritabilité (σ)	2 (1,2)	1,2 (1,9)	0,2 (0,5)	ns
Score Comport. Mot. (σ)	1,2 (1,9)	0,5 (1)	1 (2)	ns
Score Sommeil (σ)	0 (0)	0,8 (1)	0,2 (0,5)	ns
Score Appétit (σ)	3 (3,5)	1,2 (1,5)	1,5 (1)	ns
Score Zarit (σ)	41 (5,3)	28,5 (7,2)	22,5 (7,9)	0,05

MMS-E : Mini Mental State Examination ; REF : reconnaissance des émotions faciales ; NPI : Neuropsychiatric Inventory ; MA : maladie d'Alzheimer ; TAR : training of affect recognition ; ns : non significatif (p > 0,05).

Tableau 5 Évolution des performances au MMS-E, de REF et évolution des scores au NPI et au Zarit du groupe MA-Contrôle, avant et post-programme.

	Groupe MA-Contrôle (n = 4)		p-value
	T0	T1	
Score MMS-E (σ)	19,8 (1,7)	19 (1,6)	ns
Score Visages Ekman (σ)	16,2 (5,4)	16 (5,7)	ns
Temps réponse Visages Ekman (σ)	5,4s (0,8)	5,8s (0,4)	ns
Score Joie (σ)	4 (0)	3,5 (1)	ns
Temps réponse Joie (σ)	4,7s (1,2)	4,7s (1,4)	ns
Score Peur (σ)	1 (1,2)	1 (0,8)	ns
Temps réponse Peur (σ)	4,3s (0,6)	5,6s (0,7)	ns
Score Colère (σ)	2,5 (1,9)	2,5 (1,3)	ns
Temps réponse Colère (σ)	6,7s (1,2)	6,2s (0,5)	ns
Score Tristesse (σ)	1,2 (1)	1,5 (1,3)	ns
Temps réponse Tristesse (σ)	5,3s (0,6)	6,3s (0,7)	< 0,01
Score Dégoût (σ)	2,5 (1,3)	1,8 (1,3)	ns
Temps réponse Dégoût (σ)	6,3s (1,1)	6,5s (0,5)	ns
Score Surprise (σ)	2,2 (1)	3,5 (0,6)	0,09
Temps réponse Surprise (σ)	4,9s (1,7)	4,8s (1,3)	ns
Score Neutre (σ)	2,8 (1)	2,2 (1,3)	ns
Temps réponse Neutre (σ)	5,4s (1,2)	6,3s (0,8)	ns
Score NPI Total (σ)	25,8 (13,8)	27 (17,4)	ns
Score Idées délirantes (σ)	2 (2,3)	3 (2,6)	ns
Score Hallucination (σ)	0 (0)	0 (0)	ns
Score Agitation (σ)	3 (2,6)	2,5 (3)	ns
Score Dépression (σ)	3 (2,6)	2 (1,6)	ns
Score Anxiété (σ)	5 (2)	4,8 (2,5)	ns
Score Euphorie (σ)	0,5 (1)	1 (1,2)	ns
Score Apathie (σ)	5,8 (3,3)	5 (3,8)	ns
Score Désinhibition (σ)	0 (0)	0,2 (0,5)	ns
Score Irritabilité (σ)	3,8 (1,7)	2 (2,7)	0,07
Score Comport. Mot. (σ)	1,8 (2,1)	3 (3,8)	ns
Score Sommeil (σ)	0,2 (0,5)	0,2 (0,5)	ns
Score Appétit (σ)	0,8 (1)	3,2 (2,5)	ns
Score Zarit (σ)	25,2 (16,9)	29,8 (16,5)	ns

MMS-E : Mini Mental State-Examination ; REF : reconnaissance des émotions faciales ; NPI : Neuropsychiatric Inventory ; MA : maladie d'Alzheimer ; ns : non significatif ($p > 0,05$).

Fonctionnement cognitif

Les scores au MMS-E sont restés similaires au cours des évaluations pour les deux groupes (comparaisons T0 vs T1, T1 vs T2, T0 vs T2 ; tous $p > 0,05$).

Performances de REF

Pas de changement significatif au score total des visages d'Ekman de T0 à T1 pour les deux groupes (tous $p > 0,05$). Une tendance à l'amélioration des performances ($p = 0,09$) était retrouvée pour le groupe MA-TAR de T0 à T2, avec une augmentation de 12 % des performances. Qualitativement, les performances avaient augmenté de 11 % entre T0 et T1, alors qu'une baisse de 2 % était observée pour le groupe MA-Contrôle. En détail, les progrès de REF du groupe MA-TAR concernaient surtout la tristesse (amélioration de +133 %, T0 vs T1 $p = 0,09$; T0 vs T2 : $p < 0,05$), et la peur (amélioration de +63 %, T0 vs T1, $p > 0,05$). Le groupe MA-TAR était devenu plus rapide pour reconnaître les émotions,

particulièrement pour la tristesse, le dégoût et la condition neutre (tous $p < 0,05$). Pour le groupe MA-Contrôle, seule une augmentation des temps de réponse pour la tristesse était observée (T0 vs T1 $p < 0,01$).

Stratégies de regard durant la REF

De nombreuses modifications des stratégies de regard ont été observées au sein du groupe MA-TAR (Tableau 6). Globalement, les temps moyens de fixation sur les visages étaient augmentés ($p < 0,05$), surtout pour la joie et la tristesse. Les résultats montraient aussi une augmentation de l'observation (nombre de fixations et/ou durée moyenne d'une fixation et/ou temps d'observation et/ou % d'observation) des yeux pour la tristesse et le dégoût ; du nez pour la joie, la surprise et la peur ; des yeux et du nez pour la colère (Fig. 5), tous $p < 0,05$. Ces modifications se maintenaient à distance du programme (comparaisons T0 vs T2, $p < 0,05$) à l'exception de la tristesse, pour laquelle

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Tableau 6 Différences significatives des comportements d'observation visuelle (nombres et durées des fixations oculaires) pendant la reconnaissance des émotions faciales aux visages d'Ekman du groupe MA-TAR, avant, post et un mois post-programme.

Groupe MA-TAR (n = 4)						
	T0	T1	T2	p-value T0 vs T1	p-value T1 vs T2	p-value T0 vs T2
Total						
Temps moyen d'une fixation sur le visage (σ)	253 ms (15)	306 ms (22)	314 ms (29)	0,05	ns	<0,05
Joie						
Temps moyen d'une fixation sur le visage (σ)	236 ms (26)	293 ms (32)	303 ms (47)	<0,01	ns	<0,05
% d'observation RI nez (σ)	14,2 (13,2)	46,8 (17,5)	35,5 (15)	<0,05	ns	ns
Nombre de fixations RI nez (σ)	0,7 (0,4)	4,1 (1,8)	3,2 (2,9)	<0,05	ns	ns
Temps moyen d'une fixation RI nez (σ)	189 ms (39)	289 ms (18)	310 ms (69)	<0,01	ns	<0,05
Temps d'observation RI nez (σ)	123 ms (46)	1199 ms (592)	1030 ms (1140)	<0,05	ns	ns
Peur						
Nombre de fixations RI nez (σ)	1 (0,3)	2,1 (1,5)	1,9 (0,1)	ns	ns	<0,05
Temps d'observation RI nez (σ)	236 ms (129)	590 ms (473)	564 ms (122)	ns	ns	<0,05
Colère						
% d'observation RI nez (σ)	51 (6,2)	58 (8)	64 (3)	ns	ns	0,05
Nombre de fixations RI yeux (σ)	2,7 (0,7)	4,9 (1,3)	4,5 (1)	0,05	ns	<0,05
Temps moyen d'une fixation RI yeux (σ)	253 ms (21)	311 ms (39)	355 ms (46)	<0,05	ns	<0,01
Temps d'observation RI yeux (σ)	652 ms (103)	1478 ms (384)	1560 ms (289)	<0,05	ns	<0,01
Nombre de fixations RI nez (σ)	1,6 (0,1)	2,6 (0,5)	2 (0,7)	<0,05	ns	ns
Temps d'observation RI nez (σ)	394 ms (90)	792 ms (244)	661 ms (196)	ns	ns	<0,05
Tristesse						
Temps moyen d'une fixation sur le visage (σ)	246 ms (19)	300 ms (25)	301 ms (13)	0,05	ns	<0,01
Temps moyen d'une fixation RI yeux (σ)	241 ms (42)	322 ms (39)	293 ms (11)	0,05	ns	ns
Temps moyen d'une fixation RI nez (σ)	249 ms (25)	279 ms (21)	310 ms (37)	ns	ns	<0,05
Dégout						
Temps d'observation RI yeux (σ)	841 ms (400)	890 ms (221)	1213 ms (270)	ns	ns	0,05
Surprise						
Nombre de fixations sur le visage (σ)	4,4 (0,5)	7,4 (2,3)	8,4 (2,1)	ns	ns	<0,05
Nombre de fixations RI nez (σ)	1,1 (0,7)	2,1 (0,9)	1,9 (0,3)	<0,05	ns	0,05
Temps d'observation RI nez (σ)	271 ms (184)	651 ms (375)	520 ms (179)	0,08	ns	<0,05

RI : région d'intérêt ; MA : maladie d'Alzheimer ; TAR : training of affect recognition ; ns : non significatif ($p > 0,05$).

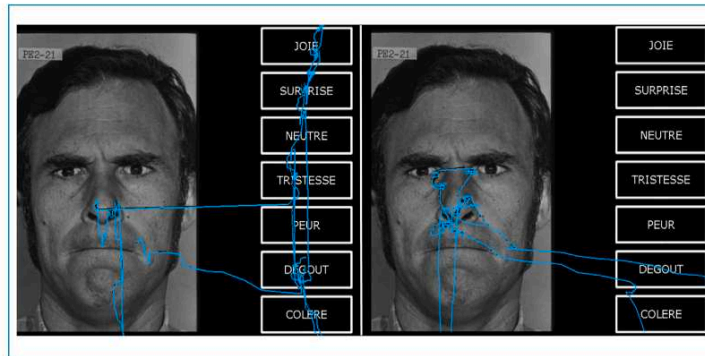


Figure 5. Exemple de tracés oculaires obtenus chez un participant du groupe maladie d'Alzheimer (MA)-training of affect recognition program (TAR) avant (à gauche) et après (à droite) remédiation de la reconnaissance des émotions faciales par le programme TAR. À la suite de la prise en charge, il y a une augmentation de l'observation des yeux.

L'augmentation de la durée moyenne de fixation n'était plus significative pour les yeux mais l'était devenue pour le nez. Aucune modification significative des stratégies de regard n'était observée pour le groupe MA-Contrôle.

Troubles du comportement et fardeau de l'aidant

Tendance à la diminution des TDC observée dans le groupe MA-TAR après la prise en charge (NPI T0 vs T1 $p=0,08$). Cette diminution était significative un mois après (T0 vs T2 $p<0,05$). En détail, les mêmes résultats étaient observés pour l'apathie et l'irritabilité (T0 vs T2 $p<0,05$). Pas de différence significative observée pour le groupe MA-Contrôle ($p>0,05$).

Diminution du fardeau de l'aidant après le programme pour le groupe MA-TAR, se maintenant un mois après (Zarit T0 vs T1 et T0 vs T2 tous $p<0,05$). Pas de modification significative du Zarit pour le groupe MA-Contrôle (T0 vs T1 $p>0,05$) (Tableaux 4 et 5 et Fig. 3).

Discussion

Les objectifs étaient de confirmer que la REF pouvait être réhabilitée dans la MA par l'utilisation du TAR, et d'étudier les conséquences de cette prise en charge sur les stratégies d'observation des visages émotionnels et sur les TDC. Les résultats montraient que les participants ayant bénéficié du TAR :

- reconnaissaient mieux et plus rapidement les émotions faciales, en particulier la tristesse, la peur et l'expression neutre ;
- avaient modifié leurs stratégies de balayage visuel des visages émotionnels avec une augmentation de l'observation de la partie supérieure du visage (nez et/ou yeux) ;
- avaient une diminution des TDC (apathie et irritabilité en particulier) et du fardeau de l'aidant.

Ces modifications se maintenaient globalement un mois après la prise en charge. Ces résultats étaient spécifiques

au TAR, puisque aucune modification significative n'a été observée dans le groupe MA-Contrôle.

Bien que nos résultats rejoignent ceux de Garcia-Casal et al. [17] avec une amélioration globale des performances de REF suite au TAR, nous notons quelques différences. Leur étude a mis en évidence une amélioration de la reconnaissance de l'expression neutre, surprise et dégoût tandis que nous avons observé une amélioration pour l'expression neutre, tristesse et peur, ces deux dernières émotions étant les plus communément altérées dans la MA [1,2]. Il semblerait que le TAR ait permis de corriger certaines confusions de reconnaissance souvent observées entre peur et surprise ou neutre et tristesse [24]. Ainsi, les progrès de reconnaissance de la peur se seraient fait au détriment de la reconnaissance de la surprise à l'évaluation T1, avant de revenir à un niveau de performance initial à l'évaluation T2.

Le TAR a eu pour effet d'importantes modifications des stratégies d'observation des visages émotionnels, avec une augmentation des durées moyennes de fixation et une observation plus importante de la partie supérieure du visage, en particulier les yeux. Il est intéressant de constater que le TAR a surtout eu des conséquences sur la reconnaissance de la colère, de la tristesse et de la peur, considérées comme émotions les plus difficiles à reconnaître et les plus reliées aux yeux [25–27]. Ces émotions sont les moins reconnues dans la MA [1,2], maladie dans laquelle la région des yeux est moins observée [5,6]. Ainsi nos données vont dans le même sens que Hot et al. [18], et soutiennent l'idée que le déficit de REF dans la MA serait lié à une modification des stratégies d'observation des visages entraînant une diminution de l'orientation de l'attention vers les yeux (perte de saillance). Dès lors que l'attention du patient est de nouveau bien orientée sur les zones-clés du visage, l'émotion peut être reconnue.

Notre étude semble confirmer le lien entre stratégies d'observations des visages, REF et TDC dans la MA [6]. Ainsi, par un effet « cascade » attendu, le TAR a permis d'améliorer la REF mais a également diminué les TDC (en particulier l'apathie et l'irritabilité) et par conséquent le fardeau de l'aidant. Elle confirme aussi le lien entre déficit de REF et fardeau de l'aidant [15], et permet d'envisager un nouveau

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type de prise en charge permettant de diminuer les TDC, retarder l'institutionnalisation et améliorer le bien-être des aidants familiaux.

Notre étude possède cependant des limites. D'abord le groupe MA-Contrôle n'a pu être évalué à T2 du fait de la pandémie de la COVID-19. De plus, étant une étude princeps, elle fut menée sur un petit échantillon de participants et a utilisé le test des visages d'Ekman ainsi que le NPI : nos résultats seront à confirmer sur un échantillon plus grand avec du matériel plus écologique (dynamique) et des échelles cliniques plus spécifiques comme la GDS pour évaluer le niveau de dépression. Enfin, nous n'avons pas effectué la correction de Bonferroni sur nos analyses statistiques. Nous avons fait le choix de présenter toutes les analyses statistiques effectuées et de ne pas corriger les p conformément à l'article de Perneger [28].

Conclusion

Cette étude confirme que la REF peut être réhabilitée dans la MA. Le TAR permet d'améliorer en particulier la reconnaissance de l'expression neutre, de la tristesse et de la peur en raison d'une modification des stratégies d'observation des visages émotionnels. Cela entraîne une diminution des TDC (apathie et irritabilité surtout) et du fardeau de l'aidant familial de manière durable, et constitue ainsi une nouvelle thérapie non médicamenteuse ciblant les TDC en améliorant les capacités de cognition sociale des patients, leur qualité de vie et celle de leurs proches.

Déclaration de liens d'intérêts

Les auteurs déclarent ne pas avoir de liens d'intérêts.

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2. Informed Consent Forms

2.1. Study 2: EYE-TAR (AD+)



Notice d'information

∞ EYE-TAR(AD+) ∞

Remédiation de la reconnaissance des émotions faciales dans la maladie d'Alzheimer et effets sur les stratégies d'observation, les troubles du comportement et le fardeau de l'aidant

Chère Madame, Cher Monsieur,

Nous vous proposons de participer à l'étude **EYE-TAR(AD+)**. Le promoteur est l'**Association de Recherche Bibliographique et Scientifique pour les Neurosciences** (AREBISN, 3 rue Niepce, 06000 Nice/représentée par le Pr Alain PESCE). Elle est menée en collaboration avec le **Laboratoire d'Anthropologie et de Psychologie cognitives et sociales de l'Université Nice Côte d'Azur** (LAPCOS, EA 7278). L'investigateur principal à Monaco est le **Dr Sandrine LOUCHART de la CHAPELLE** (Centre Mémoire, Centre de Gériologie Clinique RAINIER III, CHPG Monaco. Tel : +377 99 99 55 77)

L'étude **EYE-TAR(AD+)** est une étude observationnelle, portant sur 20 volontaires.

L'objectif : évaluer les bénéfices de l'atelier de remédiation de la reconnaissance des émotions faciales ou de l'atelier de stimulation cognitive qui vous sera proposé dans le cadre de votre prise en charge au Centre Mémoire du Centre Rainier III (CRIII). Il s'agit d'un **atelier en groupe de 5 personnes, réalisé sur une période de 6 semaines, à raison de 2 séances d'1 heure par semaine.**

Les évaluations réalisées avant, pendant et 1 mois après l'atelier sont celles réalisées en soins courants chez les patients pris en charge au Centre Mémoire du CRIII. Elles évaluent le fonctionnement cérébral (en particulier la cognition sociale), les stratégies du regard (à l'aide d'un **eye-tracking**), le comportement, et la charge de l'aidant.

Les résultats de ces évaluations font partie intégrante de votre dossier médical au CHPG. Les données nécessaires à la conduite de cette étude correspondent à ces résultats. Elles seront collectées et totalement anonymisées afin d'être analysées selon l'objectif de l'étude, au sein même de l'Unité de Recherche du CRIII.

La participation à cette étude n'entraînera aucun risque pour vous. Il s'agit d'évaluer les ateliers qui vous sont proposés. Votre participation doit être purement volontaire. Si vous décidez de ne pas y participer, cela ne changera pas votre prise en charge, vous bénéficierez des meilleurs soins possibles.

Confidentialité des données :

Le protocole de l'étude **EYE-TAR(AD+)** a été créé conformément aux Bonnes Pratiques Cliniques et la confidentialité de vos informations personnelles est garantie conformément à la loi Monégasque n°1.165 du 23 décembre 1993 modifiée relative à la protection des informations nominatives.

Si vous avez des questions au sujet du traitement de vos données au cours de cette étude, vous pouvez contacter le Délégué à la Protection des Données au CHPG : M. Samir Tordjman (Direction du Système d'Information et Organisation, 1 avenue Pasteur, 98000 Monaco. Tel : 04 92 41 68 73).

Consentement éclairé

Je soussigné(e) M., Mme (nom, prénom) : **né(e) le** __ / __ / ____

certifie avoir été informé(e) par le Dr de l'objectif de l'étude **EYE-TAR(AD+)** menée par son équipe au Centre Mémoire/Centre Rainier III, Avenue Pasteur, tel : 00377 99 99 55 90.

J'ai reçu des informations détaillées concernant les modalités de réalisation de cette étude, comprenant le recueil des données me concernant, relatives à la passation des évaluations réalisées dans le cadre de ma prise en charge.

J'accepte que mes données soient utilisées de façon complètement anonyme.

Je suis informé(e) :

- Que ma participation à cette étude ne nécessite aucun changement dans mes traitements médicamenteux, ni aucun soin supplémentaire. Cela ne modifie en rien ma prise en charge et mon suivi médical. Cela n'engendrera aucun frais supplémentaire par rapport à ceux prévus pour mon suivi habituel.
- Qu'aucun effet indésirable n'est attendu, pendant et après ma participation.
- De mon droit de refuser de participer et de mon droit à interrompre ma participation, à tout moment, sans avoir à justifier ma décision. En cas de refus, il n'y aura pas de conséquence sur la suite de ma prise en charge, ni sur la qualité des soins qui me seront prodigués.
- Que mon identité restera confidentielle et les données me concernant seront rendues anonymes. Elles ne pourront être consultées que par l'investigateur de l'étude ou les membres de son équipe désignés, ainsi que par des membres des Autorités de Santé. Je pourrai exercer mon droit d'accès, de regard et de rectification sur les données me concernant par l'intermédiaire du médecin de mon choix ou du médecin signataire.
- Que mes données personnelles seront analysées et que, tant que ces données ne seront pas encore totalement anonymisées, je peux à tout moment m'opposer à ce que ces données soient utilisées à des fins de recherche.

J'accepte de participer volontairement à cette étude.

A, le **Signature du Patient :**

A, le **Signature de l'Aidant :**

*Je confirme avoir expliqué la nature et le but de l'étude au patient mentionné ci-dessus et à son aidant.
Le patient consent à participer en signant et en datant.*

A, le **Signature du Médecin investigateur :**

Ce consentement est établi en 2 exemplaires : 1^{er} feuillet destiné au Participant & son Aidant / 2^o feuillet destiné au Médecin

2.2. Study 3: EYE-TAR (MA) Follow-up



Notice d'information

∞ EYE-TAR(MA)-Follow-Up ∞

Suivi à long terme des patients inclus dans l'étude EYE-TAR(MA) : Remédiation de la reconnaissance des émotions faciales dans la maladie d'Alzheimer et effets sur les stratégies d'observation, les troubles du comportement et le fardeau de l'aidant

Chère Madame, Cher Monsieur,

Nous vous proposons de participer à l'étude **EYE-TAR(MA)-Follow-Up** dont le promoteur est l'**Association de Recherche Bibliographique et Scientifique pour les Neurosciences** (AREBISN, 3 rue Niepce, 06000 Nice/représentée par le Pr Alain PESCE), menée en collaboration avec le **Laboratoire d'Anthropologie et de Psychologie cognitives et sociales de l'Université Nice Côte d'Azur** (LAPCOS, EA 7278), et dont l'investigateur principal à Monaco est le **Dr Sandrine LOUCHART de la CHAPELLE** (Centre Mémoire, Centre de Gériatrie Clinique RAINIER III, CHPG Monaco. Tel : +377 99 99 55 77)

L'étude **EYE-TAR(MA)-Follow-Up** est une étude observationnelle, portant sur 8 volontaires.

L'objectif : évaluer l'impact à distance de l'atelier de remédiation de la reconnaissance des émotions faciales ou de l'atelier de stimulation cognitive que vous avez suivi il y a plus de 2 ans. Et suite auquel vous aviez participé à l'étude EYE-TAR(MA).

Les données nécessaires à la conduite de cette nouvelle étude sont celles qui font partie intégrante de votre dossier médical au Centre Rainier III. Elles comprennent :

- âge, sexe, niveau d'étude, et résultats des bilans neuropsychologiques réalisés par le passé ;
- données issues des questionnaires et échelles permettant d'estimer l'impact à long terme des ateliers auxquels vous aviez participé. Leur passation dure 45 minutes maximum, réalisée au cours d'une visite au Centre Rainier III. Elles évaluent le fonctionnement cérébral (en particulier la reconnaissance des émotions), le comportement, ainsi que la charge de l'aidant.

Ces données seront collectées et totalement anonymisées afin d'être analysées selon l'objectif de l'étude, au sein même de l'Unité de Recherche du Centre Rainier III.

La participation à cette étude n'entraînera aucun risque pour vous. Votre participation doit être purement volontaire. Si vous décidez de ne pas y participer, cela ne changera pas votre prise en charge, vous bénéficierez des meilleurs soins possibles.

Confidentialité des données :

Le protocole de l'étude **EYE-TAR(MA)-Follow-Up** a été créé conformément aux Bonnes Pratiques Cliniques et la confidentialité de vos informations personnelles est garantie conformément à la loi Monégasque n°1.165 du 23 décembre 1993 modifiée relative à la protection des informations nominatives.

Si vous avez des questions au sujet du traitement de vos données au cours de cette étude, vous pouvez contacter le Délégué à la Protection des Données au CHPG : M. Samir Tordjman (Direction du Système d'Information et Organisation, 1 avenue Pasteur, 98000 Monaco. Tel : 04 92 41 68 73).

Consentement éclairé

Je soussigné(e) M., Mme (nom, prénom) :

né(e) le __ / __ / ____

certifie avoir été informé(e) par le Dr

(Centre Mémoire/Centre Rainier III, Avenue Pasteur, tel : 00377 99 99 55 90) des objectifs de l'étude **EYE-TAR(MA)-Follow-Up** menée par son équipe.

J'ai reçu des informations détaillées concernant les modalités de réalisation de cette étude, comprenant le recueil des données me concernant, relatives à la passation des évaluations réalisées dans le cadre de ma prise en charge.

J'accepte que mes données soient utilisées de façon complètement anonyme.

Je suis informé(e) :

- Que ma participation à cette étude ne nécessite aucun changement dans mes traitements médicamenteux, ni aucun soin supplémentaire. Cela ne modifie en rien ma prise en charge et mon suivi médical. Cela n'engendrera aucun frais supplémentaire par rapport à ceux prévus pour mon suivi habituel.
- Qu'aucun effet indésirable n'est attendu, pendant et après ma participation.
- De mon droit de refuser de participer et de mon droit à interrompre ma participation, à tout moment, sans avoir à justifier ma décision. En cas de refus, il n'y aura pas de conséquence sur la suite de ma prise en charge, ni sur la qualité des soins qui me seront prodigués.
- Que mon identité restera confidentielle et les données me concernant seront rendues anonymes. Elles ne pourront être consultées que par l'investigateur de l'étude ou les membres de son équipe désignés, ainsi que par des membres des Autorités de Santé. Je pourrai exercer mon droit d'accès, de regard et de rectification sur les données me concernant par l'intermédiaire du médecin de mon choix ou du médecin signataire.
- Que mes données personnelles seront analysées et que, tant que ces données ne seront pas encore totalement anonymisées, je peux à tout moment m'opposer à ce que ces données soient utilisées à des fins de recherche.

J'accepte de participer volontairement à cette étude.

A, le *Signature du Patient :*

A, le *Signature de l'Aidant :*

Je confirme avoir expliqué la nature et le but de l'étude au patient mentionné ci-dessus et à son aidant. Le patient consent à participer en signant et en datant.

A, le *Signature du Médecin investigateur :*

Ce consentement est établi en 2 exemplaires : 1^{er} feuillet destiné au Participant & son Aidant / 2^e feuillet destiné au Médecin



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