Mattioli 1885
srl- Strada di Lodesana 649/sx
Loc. Vaio - 43036 Fidenza (Parma)
tel 0524/530383
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Mattioli 1885

srl- Strada di Lodesana 649/sx
Loc. Vaio - 43036 Fidenza (Parma)
tel +39 0524 530383
fax +39 0524 82537
www.mattioli1885.com
E-mail: redazione@mattioli1885.com

Fondazione CIRNA Onlus
Piazza castello 19, 27100 Pavia
Fax 0382 520070
E-mail: cirna@cefalea.it
website: www.cefalea.it

Redazione Confinia Cephalalgica et Neurologica
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Tel.: +39.0382.984712 +39.0382.984707

Editorial Office
Valeria Ceci
E-mail: valeriaceci@mattioli1885.com

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Editorial

"In principio era il Verbo". Il ruolo della parola tra neurologia e psicoanalisi, da Jean-Martin Charcot (1825-1893) a Jacques Lacan (1901-1981)

Francesco Brigo[1], *Mariano Martini*[2]

[1]Department of Neurology, Hospital of Merano (SABES-ASDAA), Merano, Italy; [2]Department of Health Sciences, University of Genoa, Italy

"Chi falla in appuntar primo bottone, né mezzani né l'ultimo indovina".

L'espressione, tratta dalla commedia teatrale *Calendaio* (1582) del filosofo italiano Giordano Bruno (1543-1600), può essere utilizzata per sottolineare l'importanza di un corretto inquadramento diagnostico iniziale come momento essenziale per la gestione clinica complessiva del paziente.

La raccolta anamnestica rappresenta il primo e principale atto del processo diagnostico in ogni branca della medicina. In neurologia l'anamnesi riveste poi un'importanza centrale, in quanto necessaria per formulare un sospetto diagnostico iniziale in grado di correlare la sintomatologia presentata dal paziente con una specifica localizzazione anatomica. Questo sospetto iniziale di correlazione clinico-anatomica – risultante dalle informazioni raccolte tramite un'anamnesi accurata – viene poi rifinita, confermata o smentita, dall'esame obiettivo neurologico, che si configura quindi come un atto di verifica concreta e sperimentale di un'ipotesi teorica.

La centralità dell'anamnesi nell'inquadramento diagnostico in neurologia viene convenzionalmente ricondotta all'insegnamento di Jean-Martin Charcot (1825-1893) (1). Leggendo le trascrizioni delle sue lezioni condotte alla Salpêtrière, si resta stupiti nel notare come spesso Charcot formulasse i propri giudizi diagnostici basandosi quasi esclusivamente sulle informazioni raccolte dal dialogo con i pazienti, delegando l'esecuzione dell'esame fisico ai suoi collaboratori (2,3). Agli allievi egli era solito ricordare l'espressione del medico François Joseph Victor Broussais (1772-1838) secondo cui i sintomi sono il grido di dolore proprio di ciascuna malattia, sottolineando l'importanza di una accurata anamnesi incentrata sull'ascolto attento del racconto del paziente come elemento essenziale del processo diagnostico (4,5).

L'attenzione estrema all'anamnesi fu condivisa da molti collaboratori di Charcot. Tra questi vale la pena ricordare la figura di Désiré-Magloire Bourneville (1840–1909). Dai suoi contributi emerge chiaramente l'enfasi posta alla centralità della parola come strumento chiarificatore della realtà in grado di far luce sulla sede e sulle cause dei sintomi neurologici presentati dai pazienti. Questa attitudine era probabilmente alimentata dal suo impegno politico caratterizzato dalla fiera impronta repubblicana, democratica e socialista, e dalla sua ampia esperienza in ambito editoriale e giornalistico. Egli aveva infatti collaborato con numerose riviste scientifiche (tra cui il *Mouvement Médical, Panthéon de l'Industrie*, e *Le Réveil*), per poi fondare nel 1873 il *Progrès Médical*, un giornale che ebbe un ruolo chiave nella disseminazione delle teorie di Charcot, con cui, inoltre, aveva costituito nel 1880 gli *Archives de neurologie* (6,7).

Come è noto, Sigmund Freud (1856-1939) trascorse un importante periodo della propria formazione a Parigi, assistendo alle lezioni di Charcot e rimanendone profondamente impressionato. A colpire il giova-

ne Freud fu il personale approccio allo studio dell'isteria proposto dal neurologo francese. Tuttavia, sebbene forse a livello più sotterraneo (verrebbe quasi da dire in maniera *inconscia*), ciò che influenzò maggiormente Freud – e che può pertanto essere considerato il più importante e intimo punto di contatto tra la nascente ma già consolidata neurologia e la futura psicoanalisi – fu l'importanza della parola come strumento ordinatore della realtà informe e caotica del sintomo.

Due anni dopo la morte del grande neurologo francese, Freud pubblicò, insieme con Josef Breuer (1842-1925), gli *Studien* über *Hysterie* (1895). In quest'opera, il primo passo lungo la via originale e alternativa di indagine della psiche umana che sarebbe esitata nella psicoanalisi, si esalta l'importanza del dialogo come porta d'accesso alle profondità e complessità dell'inconscio umano e al contempo come efficace mezzo di cura. Preso atto dell'impossibilità euristica e gnoseologica della psicologia meccanicistica e biologica del suo tempo (*Entwurf einer Psychologie*, 1895), Freud vide nel linguaggio la luce con cui rischiarare le oscurità della psiche umana. In questo, egli rappresentò l'esempio estremo (e forse ultimo) di una ragione che nel suo procedere cartesiano e quasi algebrico è in grado di dare forma all'informe, imponendo ordine e struttura al caos, ergendosi vittoriosa dopo essere scesa, impavida e sicura, a sfidare e smuovere le profondità dell'inconscio umano (*"Flectere si nequeo superos, Acheronta movebo"*, *Die Traumdeutung*, 1899). La figura 1 mostra lo studio nel quale Freud visitava i propri pazienti. Sopra il famoso divano è possibile notare una litografia realizzata nel 1888 da Eugène Louis Pirodon (1824–1908) che riproduce l'opera *Une leçon clinique du Dr Charcot à la Salpêtrière* (1887) del pittore francese André Brouillet (1857-1914) (figura 2). Nella scena raffigurata Charcot esamina una paziente, illustrandone le caratteristiche cliniche di fronte ad un ampio uditorio. Il maestro francese non ha alcun contatto fisico con la giovane donna, la celebre Marie "Blanche" Wittman (1859-1913), affetta da isteria, che è invece sorretta da Joseph Babiński (1857-1932), che fu il vero sistematizzatore della moderna semeiotica neurologica (8,9). Il fatto che Freud conservasse un'immagine come questa nello spazio dove esercitava la propria pratica clinica è un'ulteriore dimostrazione del profondo legame non solo personale ma professionale che lo univa a Charcot. Un legame quasi metodologico accomunato dal rilievo dato alla parola come elemento centrale nella relazione medico-paziente, e che – nelle sfumature di senso, nella scelta dei vocaboli o nell'utilizzo di metafore – esprime la complessità del vissuto di malattia e la sua percezione soggettiva da parte del malato, ma anche l'interpretazione datane dal medico (10).

Figura 1: Il famoso divano di Freud, custodito presso il Freud Museum di Londra. Sopra di esso è collocata la litografia di Eugène Louis Pirodon (1824–1908) che riproduce l'opera *Une leçon clinique du Dr Charcot à la Salpêtrière* (1887) del pittore francese André Brouillet (1857-1914). © 2018 Freud Museum London.

Figura 2: *Une leçon clinique du Dr Charcot à la Salpêtrière* (1888), litografia di Eugène Louis Pirodon (1824–1908) di proprietà di Sigmund Freud, ora custodita presso il Freud Museum di Londra. © 2018 Freud Museum London.

È curioso ricordare come inizialmente Freud fosse solito raccogliere l'anamnesi (che per lui aveva il significato autentico di reminiscenza, di scavo quasi archeologico nel passato individuale) esercitando una leggera pressione sulla fronte del paziente sveglio e rilassato. Successivamente abbandonò del tutto tale contatto fisico, affidandosi unicamente al potere invisibile della parola (11).

La centralità della parola come strumento chiarificatore della realtà, ereditata dal maestro Charcot, passò poi da Freud a Jacques Lacan (1901-1981). Per lo psicoanalista francese la psiche è strutturata come un linguaggio, e quindi accessibile e indagabile mediante gli strumenti messi a disposizione dalla linguistica strutturale di Ferdinand de Saussure (1857-1913). Ma con Lacan la forza della parola si infrange di fronte alla moderna – e già, verrebbe da dire, postmoderna – crisi e fuga del senso. I meccanismi del sogno freudiano vengono reinterpretati dallo psicoanalista francese mediante le figure retoriche della metafora e della metonimia (12). Tuttavia, pur rappresentando una sostituzione e spostamento continui di significato, esse costituiscono un tentativo asintotico di raggiungere e de-finire la realtà in-finita e in-definita, fluida e sempre sfuggente del *Senso*. Noi, soggetti del linguaggio, crediamo di parlare, ma in realtà – ci dice Lacan – "siamo parlati" dall'agire impersonale, culturalmente costruito, del "grande Altro" (13). La crisi della parola diventa quindi crisi del senso.

Se la psicoanalisi di Lacan, come propaggine estrema e per certi aspetti antitetica della cristallina psicologia dinamica proposta da Freud, valorizza e al contempo sottolinea i limiti della parola come strumento conoscitivo e di comunicazione del reale, la neurologia continua a vedere in essa il fondamento del proprio metodo. Un metodo in cui il processo diagnostico si configura come l'analogo clinico del processo di verifica scientifica di un'ipotesi, ma in cui la raccolta anamnestica era e continua a rimanere un'arte. Un'arte frutto di esperienza e competenza personali, ma non priva di regole né immune da sistematizzazione. L'anamnesi permette infatti – in una prospettiva di medicina basata sulle prove di efficacia (*evidence-based medicine*) e sulla statistica bayesiana – di rifinire la probabilità iniziale di malattia raccogliendo informazioni che consentano di intraprendere un percorso diagnostico mediante ulteriori indagini strumentali per giungere alla diagnosi finale (14,15).

Il processo diagnostico in neurologia è un percorso affascinante, talora dalla complessità quasi labirintica, che nasce dalla parola e che termina nella parola, scaturisce da una domanda (*"Quali sono i suoi disturbi?"*) e si completa, trovando il suo personale *senso*, con una risposta.

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Bibliografia

1. Brigo F, Martini M, Lorusso L. The Italian contribution to the anatomo-clinical method and physical examination in the history of neurology. Conf. Cephalal. et Neurol. 2022; Vol. 32, N. 3: e2022024
2. Brigo F, Lattanzi S, Martini M, Bragazzi N, Nardone R, Walusinski O. "Spreading the word of the master": the contribution of Italian physicians in the early dissemination of Jean-Martin Charcot's theories. Neurol Sci. 2020 Dec;41(12):3787-3794.
3. Brigo F. Jean-Martin Charcot (1825-1893) and his second thoughts about hysteria. Arq Neuropsiquiatr. 2021 Feb;79(2):173-174.
4. Brigo F, Martini M. "Chi l'ha detto?". Un caso emblematico di errata attribuzione. Nuova Rivista Italiana di Storia della Medicina, Vol. 1, 2022, pp.39-50. [ISSN: 2724-4954]
5. Martini M, Brigo F, Orsini D. Medical Humanities & Tuberculosis: thinking with Stories during Recent Years. Med Sec. 2022-3 *Supplement* (in press)
6. Brigo F, Lattanzi S, Trinka E, Nardone R, Bragazzi NL, Ruggieri M, Martini M, Walusinski O. First descriptions of tuberous sclerosis by Désiré-Magloire Bourneville (1840-1909). Neuropathology. 2018 Dec;38(6):577-582.
7. Coutinho L, Walusinski O, Teive HAG. Désiré Bourneville: A Socialist in Charcot's Inner Circle. Eur Neurol. 2022;85(1):79-84.
8. Brigo F, Balasse A, Nardone R, Walusinski O. Jean-Martin Charcot's medical instruments: Electrotherapeutic devices in La Leçon Clinique à la Salpêtrière. J Hist Neurosci. 2021;30(1):94-101.
9. Brigo F, Lattanzi S, Nardone R. The Babinski sign in the first Italian reports. Neurol Sci. 2021;42(6):2595-2598.
10. Coschignano S. Conceptual metaphors and framing in Cognitive Linguistics, Conf Ceph et Neurol., (in questo numero, 2022).

11. Veggetti Finzi S. Storia della psicoanalisi: autori, opere, teorie 1895-1990. Mondadori, 2017
12. Lacan Jacques. Scritti. Volume 1. Edizione italiana a cura di Giacomo Contri. Einaudi, 2002.
13. Žižek Slavoj, Leggere Lacan. Guida perversa al vivere contemporaneo. Bollati Boringhieri ed. 2009.
14. Martini M *(a cura di), Stop TB.* Ti racconto la Tibbicì. Licosia ed, Ogliastro Cilento (2020), pp.9-14.
15. Iorio S, Cilione M, Martini M, Tofani M, Gazzaniga V. Soft Skills Are Hard Skills—A Historical Perspective. Medicina *(Kaunas, Lithuania).* 2022 Aug 3;58(8):1044. doi: 10.3390/medicina58081044.

Correspondence:
Mariano Martini
Department of Health Sciences – University of Genoa
Largo R. Benzi, 10 – Pad . 3, Genova
E mail mariano.yy@gmail.com; mariano.martini@unige.it

Unbiased research is needed for rational translation of essential oils in clinic

Damiana Scuteri[1,2], Laura Rombolà[3], Luigi Antonio Morrone[3*], Shinobu Sakurada[4], Tsukasa Sakurada[5], Paolo Tonin[2], Giorgio Sandrini[6], Giacinto Bagetta[1], Maria Tiziana Corasaniti[7]*

[1]Pharmacotechnology Documentation and Transfer Unit, Preclinical and Translational Pharmacology, Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Rende, Italy; [2]Regional Center for Serious Brain Injuries, S. Anna Institute, Crotone, Italy; [3]Preclinical and Translational Pharmacology, Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Rende, Italy; [4]Department of Physiology and Anatomy, Tohoku Pharmaceutical University, Sendai, Japan; [5]Department of Pharmacology, Daiichi University of Pharmacy, Fukuoka, Japan; [6]Department of Brain and Behavioral Sciences, University of Pavia, IRCCS C. Mondino Foundation Neurologic Institute, Pavia, Italy; [7]Department of Health Sciences, University "Magna Graecia" of Catanzaro, Catanzaro, Italy.

Abstract. The use of complementary and integrative therapies is steadily growing though the quality of clinic evidence for the use of essential oils is hampered by several methodological biases. Lack of rigorous methodology in clinical studies with aromatherapy originates poor quality evidence and scientific response to overcome the biases of this field of research is needed. Accordingly, here we display a possible step-by-step preclinical-to-clinical pathway, that was followed for the essential oil of bergamot (BEO), to overcome typical biases of research in the field of essential oils, in order to provide good quality body of evidence.

Key words: bias, clinical aromatherapy, bergamot essential oil, NanoBEO, severe dementia, pain, agitation, I-MOBID-2, CONSORT.

Poor clinical research on natural products

The Food and Drug Administration (FDA) classifies essential oils for aromatherapy as cosmetic formulations. This is in line with the poor methodological rigor of clinic research in this field as well as in the field of nutraceuticals (1) and of neuroprotective agents in general (2), impeding to draw any definite conclusions about efficacy and safety of these interventions for clinical translation. In fact, in spite of the continuously growing market of natural products and the increasing use of integrative medicine, advances to provide high quality evidence for the translational and clinic use of these products is needed. The poor quality of preclinical research contributes to the biased clinical research (3). One of the fields in which aromatherapy is widely studied is that of behavioral disturbances, often during dementia. In fact, dementia has a remarkable global burden since 55 million people suffer from this neurodegenerative disease, getting even more important during the Coronavirus disease (COVID)-19 pandemic since it increases the risk of death of these patients (4). Dementia, of which Alzheimer's disease (AD) is the most common form, is fundamentally linked to the development of neuropsychiatric symptoms (NPS) in about 97% patients that worsen their health-related quality of life (HRQL) (5). NPS and agitation in particular are tightly associated to unrelieved pain that undergoes altered processing in aging (6). In fact, up to 80% nursing home elderly, that represent the population most

affected by AD, present age-related comorbidities associated with chronic pain as rheumatic conditions (7-9), low back pain (10), stroke (11), post-herpetic neuralgia and diabetic or chemotherapy-induced neuropathies (12). It is under diagnosed and under treated, also in the community setting (13-15), because cognitive deterioration impairs the self-report skills (16). Agitation is treated with atypical antipsychotics that are linked to increase up to almost double of risk of death for cardiocerebrovascular accidents (17). Due to the evident correlation between development of resistant agitation and unrelieved chronic pain and since pain severity is associated with NPS and with the use of antipsychotics (18), analgesic therapy has been tested resulting to provide effective management of agitation (19). Analgesia is the most efficacious treatment for the management of NPS (20) and it reduces the need for antipsychotics (21, 22), Therefore, aromatherapy and integrative medicine gains interest in this field, although no evidence for efficacy can be drawn, also according to Cochrane systematic review, for the methodological flaws of clinical trials (23, 24).

Biased studies

Conducting a search on PubMed/MEDLINE applying the filters to retrieve randomized clinical trials published in the last 5 years up to June 28th, 2022 with the query string "aromatherapy AND dementia" 7 results are obtained (25-31) (figure 1).

Within the studies retrieved several sources of bias occur. The study by Mascherona and collaborators enrolls 32 patients (n=16 for the control and n=16 for the intervention) to investigate the effects of aromatherapy by environmental diffusion complemented with standard psychotropic therapy and Pro Re Nata (PRN) in comparison with standard psychotropic therapy and PRN alone on NPS (29). Aromatherapy by environmental diffusion has the intrinsic bias of not allowing titration of the active components of the phytocomplex used and to prevent exact reproducibility because the concentration can be subjected to modifications also due to the different environmental conditions. Moreover, aromatherapy permits the identification by the patients and the operators of the intervention, since essential oils are endowed with strong

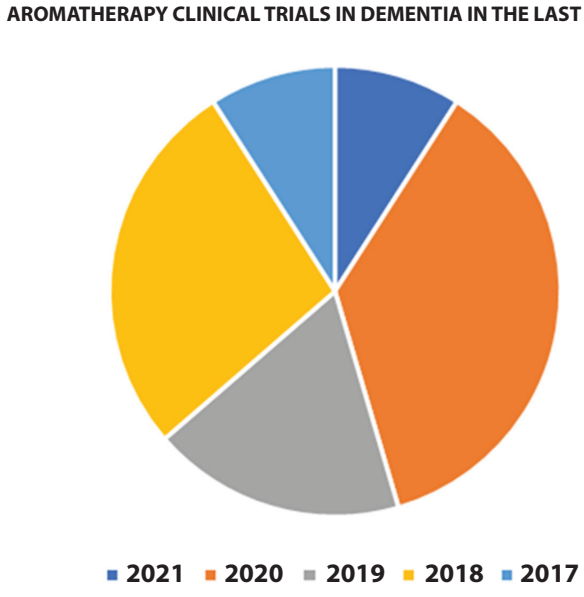

Figure 1. Randomized clinical trials retrieved from PubMed/MEDLINE in the last five years using the search string "aromatherapy AND dementia" (date of last search June 28th, 2022).

aroma, thus inducing concealment and reporting biases. Aromatherapy and massages are used also in the studies of Dimitriou and colleagues (25, 26) and in the study by Takahashi and collaborators (30) and the trial by Watson et al. (31) used a cotton patch attached the cloth to the participants collar area. The study by Fung et al., (27) uses a multicomponent aroma-massage and the study by Kozuki and coworkers uses aroma oil as a bath salt (28). Another source of bias is represented by the high possibility of essential oils to undergo degradation, causing the change of concentration of the active ingredients content. Furthermore, the samples do not always result from a rational calculation, and they are often small.

Alzheimer's disease (AD) and related agitation

Alzheimer's disease (AD) is the most common type of dementia, accounting for two thirds of total cases (32, 33). Among the several disturbances characterizing dementia, some of the most widely known are cognitive deficits and memory impairment, but 97%, thus almost the totality, of patients develops fluctuant neuropsychiatric symptoms (NPS), known as behavioral and psychological symptoms of dementia (BPSD), during the course of the disease and even before its onset (5). The latter disturbances, according to the International Psychogeriatric Association (IPA), are "a heterogeneous range of psychological reactions, psychiatric symptoms and behavior occurring in people with dementia of any etiology" (34, 35), often causing institutionalization (36). AD is a continuum characterized by an insidious onset and a median increase of the Neuropsychiatric Inventory (NPI) score at 5 years from diagnosis is reported (37); in particular, NPS can represent an under-recognized risk factors for AD development (38). Decreased motivation and affective dysregulation (39) characterize prodromal mild behavioral impairment (39, 40). People suffering from moderate-to-high depressive symptoms have been reported to be at increased risk to develop mild cognitive impairment (MCI) (41, 42). In fact, MBI represents the development of NPS in physiological aging, or in people with subjective concerns of cognitive decline (SCD) or suffering from MCI as at-risk state for incident cognitive decline and dementia (43). In particular, NPS in course of MCI are fluctuating and consist in apathy, depression, agitation, delusions, hallucinations, and sleep disorders that represent a higher risk of conversion to dementia (44). Depression in MCI doubles the risk to develop dementia (45). The severity of dementia has been correlated with hyperactivity, psychosis, affective symptoms and apathy (46). Moreover, the severity of cognitive decline is related to psychosis (47) and increase over time of agitation, disinhibition, irritability and aberrant motor behavior (48). Correlates of intracerebral pathology in course of mild, predementia symptoms can be highlighted by the progresses in structural and functional neuroimaging and in the biochemical analysis of cerebrospinal fluid occurred during the last decade (49). In fact, spatial patterns of neuroimaging biomarker change highlighted that amyloid beta (Aβ) increase significantly already 22 years before symptoms along with glucose metabolism decrease, as demonstrated in a study on rare genetic mutations (50). Also metabolomics highlighted the involvement of altered metabolism of branched-chain amino acids in AD (51). Agitation is one of the most challenging NPS and it can be induced by several triggers and as response to different situations of discomfort (52) including: depression (53), disturbance of the night-time sleep pattern (54, 55), constipation (56) and changes in environment, over or under stimulating (57). Moreover, the use of drugs as benzodiazepines in dementia deserves caution since they can exacerbate these symptoms (58, 59). Also, sensory impairment, acute medical illness (e.g., infections, respiratory diseases, urinary retention, renal failure and hospitalization), or metabolic changes, psychological distress, including delirium and depression, and the reduction of natural light in the evening in the case of sundowning syndrome, can induce agitation (60-63). Depression and anxiety are more frequent in younger patients; on the contrary, agitation, disinhibition, irritability, and aberrant motor behavior together with psychosis increase over time with the severity of dementia (48). Low socioeconomic status is a risk factor for the development of dementia and a population- and register-based cross-sectional study investigated the correlation of dementia diagnosis and cognitive stages at diagnosis (MCI, mild, moderate, or severe

dementia) with age group, sex, region of residence, household type and therapy (64). It shows that the socioeconomic status influences the referrals for diagnostic evaluation for dementia and these patients are often women, with lower educational level and multiple medical conditions (64).

Current treatments for AD-related agitation and the role of analgesia

Disease-modifying drugs are still lacking, in spite of the recent accelerated approval of aducanumab [35] by the Food and Drug Administration (FDA). Therefore, the current symptomatic anti-AD therapy against cognitive decline consists in acetylcholinesterase inhibitors and the low affinity non-competitive N-methyl-D-aspartate (NMDA)-receptor antagonist memantine, according to the Mini-Mental State Examination (MMSE) score. In the highest majority of cases, AD occurs in patients ≥ 65 years old, not being part of physiological aging (65). Therefore, affecting mainly the population of the elderly, it overlaps with age-related comorbidities responsible for chronic pain (66): musculoskeletal pain, including inflammatory arthritis, osteoarthritis and disorders related to soft tissues (67); diabetes with diabetic peripheral neuropathy and peridiabetic lesions (68) as neurological complications of diabetes; herpes zoster and post-herpetic neuralgia, being a common sequela of dermatomal rash in the older adult (69); advanced cancer and breakthrough pain (70). Aging can impact pain processing and a tight correlation between behavioral disorders, particularly agitation, and inadequate pain relief has been demonstrated (71-73). Indeed, analgesia is more effective than other treatments of agitation (20), that can be significantly reduced by means of appropriate pain treatment and regular review of therapy (21, 22). In particular, oral non-steroidal anti-inflammatory drugs (NSAIDs) including naproxen, ibuprofen and diclofenac are used for inflammatory musculoskeletal pain, while celecoxib for the treatment of chronic osteoarthrosis, after failure of acetaminophen, only for short periods as recommended by the American Geriatric Society (AGS) panel (74, 75), to reduce the gastrointestinal, renal and cardiovascular adverse reactions (76-78) and with caution in case of warfarin concurrent use (79). Gabapentin/pregabalin (80) are indicated for the treatment of neuropathic pain; serotonin-noradrenaline reuptake inhibitors (SNRIs, i.e. duloxetine, venlafaxine) (81) can be used, but not tricyclic antidepressants (TCAs, e.g. amitriptyline) due to their cardiovascular contraindications (82). Tramadol, tapentadol, buprenorphine or transdermal fentanyl after effective dose titration can be required for the treatment of severe chronic pain conditions (83, 84), following the paradigm "start low and go slow" (85), considering liver and/or renal failure. The pivotal role of chronic pain in the development of agitation is supported by the evidence that adherence to symptomatic treatment targeted towards cognitive decline can delay the onset, but not prevent the development of agitation (86). Up to 80% of patients suffering from dementia during their stay in long-term care facilities experiences pain (87). In particular, non-verbal, severely demented patients often receive insufficient pain treatment (19), due to impaired communication skills that make pain diagnosis and assessment more difficult than in cognitively intact peers (88). Moreover, the oldest old, mainly stroke survivors and cognitively impaired (11), generally are excluded from clinical trials (89), particularly for migraine (90-92). The only approved treatment for agitation is represented by the use (for no longer than 6-12 weeks) of the atypical antipsychotic risperidone (21, 93-95). Nevertheless, the use of neuroleptics in this fragile population is known to double the risk of death for cardiocerebrovascular accidents (17). An effective and safe therapy for agitation is not available yet. *Melissa officinalis* and *Lavandula officinalis*, two phytocomplexes in the form of essential oil, have proven some efficacy in the management of agitation (21). Despite this, the quality of the latter evidence is hampered because of methodological biases, as it is the case for all essential oils used in aromatherapy clinical trials, (23); accordingly, no definite conclusion about the efficacy of intervention with essential oils in dementia can be drawn (23, 96). In fact, already two decades ago (24) lack of adequate methodology in clinical studies was underlined, and in face of the increased number of trials investigating aromatherapy (figure 4) their level of certainty has not significantly improved and effort is still scarce in the study of pharmacokinetic interactions (97). A search for clinical trials has been conducted (date of last search May 17th, 2022) screening the database PubMed/MEDLINE for the following search queries: "aromatherapy", "essential

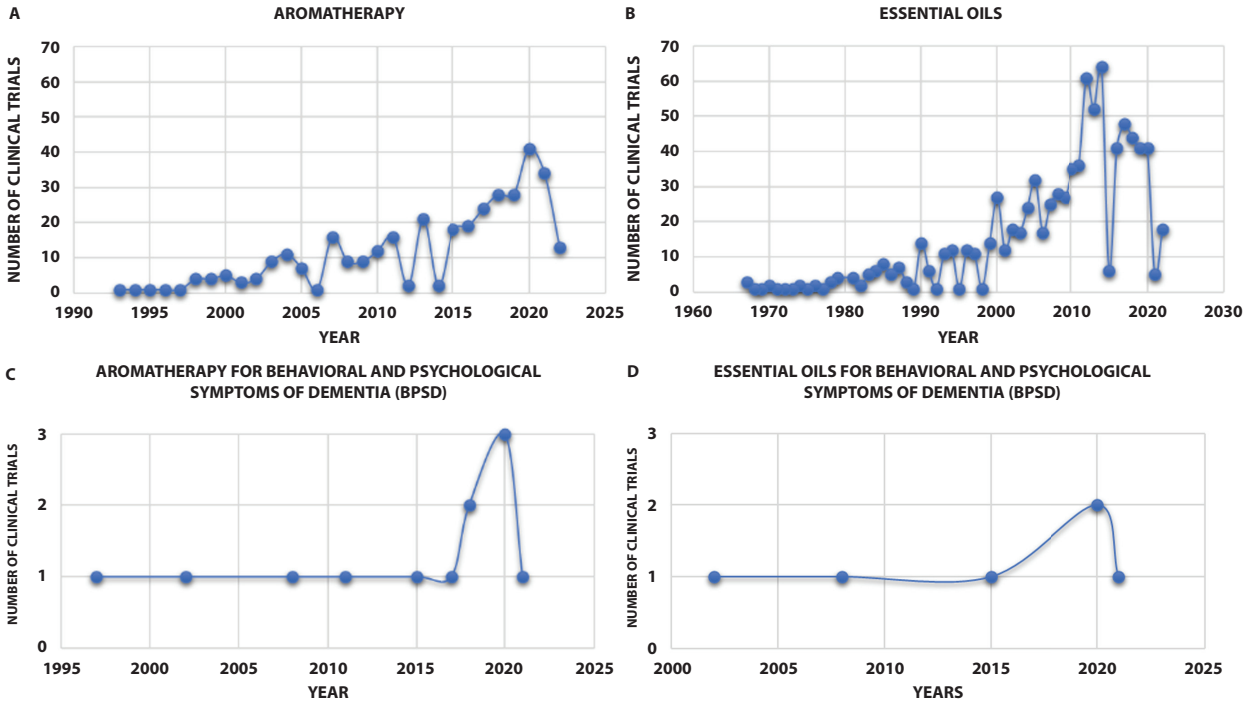

Figure 2. Clinical trials investigating aromatherapy/essential oils and behavioral and psychological symptoms of dementia since PubMed/MEDLINE inception (date of last search May 17th, 2022).

oils", "aromatherapy AND behavioral and psychological symptoms of dementia", "essential oils AND behavioral and psychological symptoms of dementia". According to the retrieved results, 345 clinical trials have investigated aromatherapy since 1993, up to a peak per year of 41 in 2020 (figure 2a), and only 12 of these where concerned with neuropsychiatric symptoms often called behavioral and psychological symptoms of dementia (BPSD) (figure 2b). The latter observation is strengthened when considering the finding that use of essential oils, are tested in 866 clinical trials from 1967 to present with a peak of 64 in 2014 (figure 2c), among which only 6 regard BPSD (figure 2d), supports the lack of improvement in this field.

Engineering of the essential oils allows to overcome the biases of aromatherapy clinical trials

Agitation in course of dementia can be due to unrelieved pain, hence it can be safely managed through analgesia. For the reasons discussed above, *Melissa officinalis* and *Lavandula officinalis* control of agitation is not conclusive and, more importantly, they do not show strong preclinical analgesic properties. Therefore, an essential oil proving antinociceptive action in experimental pain modelling clinic conditions can represent the best option for clinical translation into the management of AD-related agitation. Cannabinoids deserve attention in the field of pain, dementia and stroke (98, 99). The taxonomy, origin, biodiversity and phylogeny of the *Citrus* species is very complex, diversifying during the late *Miocene* epoch (100) and within this genus the essential oil of bergamot (BEO), classified as *Citrus bergamia*, Risso belonging to the *Rutacee* family, is a hybrid late in phylogeny likely originated in the southern part of Italy and, in particular, in Calabria (101, 102). In agreement with the *Farmacopea Ufficiale Italiana* it is obtained by cold pressing of the epicarp and, partly, of the mesocarp of the fresh fruit (103). The oxygenated compounds mainly responsible for its pharmacological activity are linalool, linalyl acetate and the terpene limonene (104) contained in the volatile fraction. BEO is the sole to have proven sound, rigorous, preclinical evidence of analgesic efficacy both in acute, inflammatory (105) and neuropathic

(106, 107) pain, but also in the formalin test relevant to clinic conditions due to its central sensitization mechanisms based on the criteria for critical appraisal of preclinic research (108, 109). Moreover, BEO is endowed with anxiolytic-like effects devoid of sedative action of diazepam and benzodiazepines in general (110), linked to the modulation of serotonergic mechanisms in the animal behavioural tasks Open Field Test, Elevated Plus Maze Test and Forced Swimming Test (111). The phytocomplex deprived of bergapten to avoid phototoxicity (112) is encapsulated in a nanotechnology delivery system based on solid lipid nanoparticles (SLN), NanoBEO (113). SLN are enriched with the anti-oxidant α-tocopherylstearate (α-TFS-SLN), to entrap the aroma, and they are incorporated into a cream for transdermal administration. This technological manipulation allows to maintain the antinociceptive and antiallodynic properties of BEO solving the issues of trials in aromatherapy to prove clinical efficacy and safety affording: 1) titration of the active principles; 2) increased stability to heat and light and consequent prevention of the degradation of the active components. This aspect is fundamental since the different active principles are responsible for the analgesic effects of BEO (114, 115); 3) reproducibility of effects thanks to constant concentration; 4) double-blind clinical trials are allowed because aroma is entrapped making NanoBEO and placebo cream indistinguishable. NanoBEO cream is dispensed through an airless dispenser preventing degradation and allowing feasibility of exact dosing (116). Furthermore, NanoBEO proves efficacy on scratching behavior that is a typical NPS. NanoBEO is patented (EP 4003294) and its efficacy and safety on agitation and pain in patients aged over 65 with severe AD is now under investigation in the first high-quality, registered (NCT04321889) (117) actually recruiting randomized, double-blind, placebo-controlled clinical trial adequately powered (n=134 patients are going to be enrolled) and following the Consolidated Standards of Reporting Trials (CONSORT) (118) statements. Since severe dementia impairs the self-report of pain the Italian version of the Mobilization–Observation–Behaviour–Intensity–Dementia (I-MOBID2) (119) recently validated in the Italian setting is going to be used to guarantee an accurate evaluation of musculoskeletal and visceral pain and to unravel even concealed pain conditions because of the execution of five guided movements (120, 121). The present step-by-step preclinical-to-clinical pathway can form the rational basis for a definite, effective and safe treatment of agitation treatment for the fragile population affected by severe AD.

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References

1. Scuteri D, Rombolà L, Watanabe C, Sakurada S, Corasaniti MT, Bagetta G, et al. Impact of nutraceuticals on glaucoma: A systematic review. Progress in brain research. 2020;257:141-54.
2. Nucci C, Martucci A, Giannini C, Morrone LA, Bagetta G, Mancino R. Neuroprotective agents in the management of glaucoma. Eye (London, England). 2018;32(5):938-45.
3. Scuteri D, Hamamura K, Sakurada T, Watanabe C, Sakurada S, Morrone LA, et al. Efficacy of Essential Oils in Pain: A Systematic Review and Meta-Analysis of Preclinical Evidence. Frontiers in pharmacology. 2021; 12:640128.
4. Scuteri D, Matamala-Gomez M, Bottiroli S, Corasaniti MT, De Icco R, Bagetta G, et al. Pain Assessment and Treatment in Dementia at the Time of Coronavirus Disease COVID-19. Frontiers in neurology. 2020;11:890.
5. Steinberg M, Shao H, Zandi P, Lyketsos CG, Welsh-Bohmer KA, Norton MC, et al. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. International journal of geriatric psychiatry. 2008;23(2):170-7.
6. Scuteri D, Berliocchi L, Rombolà L, Morrone LA, Tonin P, Bagetta G, et al. Effects of Aging on Formalin-Induced Pain Behavior and Analgesic Activity of Gabapentin in C57BL/6 Mice. Frontiers in pharmacology. 2020;11:663.
7. Burckhardt CS. The use of the McGill Pain Questionnaire in assessing arthritis pain. Pain. 1984;19(3):305-14.
8. Roche PA, Klestov AC, Heim HM. Description of stable pain in rheumatoid arthritis: a 6 year study. The Journal of rheumatology. 2003;30(8):1733-8.
9. Koop SM, ten Klooster PM, Vonkeman HE, Steunebrink LM, van de Laar MA. Neuropathic-like pain features and cross-sectional associations in rheumatoid arthritis. Arthritis research & therapy. 2015;17(1):237.

10. Deyo RA, Dworkin SF, Amtmann D, Andersson G, Borenstein D, Carragee E, et al. Report of the NIH Task Force on research standards for chronic low back pain. The journal of pain. 2014;15(6):569-85.
11. Scuteri D, Mantovani E, Tamburin S, Sandrini G, Corasaniti MT, Bagetta G, et al. Opioids in Post-stroke Pain: A Systematic Review and Meta-Analysis. Frontiers in pharmacology. 2020;11:587050.
12. Abbott CA, Malik RA, van Ross ER, Kulkarni J, Boulton AJ. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. Diabetes care. 2011;34(10):2220-4.
13. Scuteri D, Piro B, Morrone LA, Corasaniti MT, Vulnera M, Bagetta G. The need for better access to pain treatment: Learning from drug consumption trends in the USA. Functional Neurology. 2017;32(4):229-30.
14. Scuteri D, Garreffa MR, Esposito S, Bagetta G, Naturale MD, Corasaniti MT. Evidence for accuracy of pain assessment and painkillers utilization in neuropsychiatric symptoms of dementia in Calabria region, Italy. Neural regeneration research. 2018;13(9):1619-21.
15. Scuteri D, Vulnera M, Piro B, Bossio RB, Morrone LA, Sandrini G, et al. Pattern of treatment of behavioural and psychological symptoms of dementia and pain: evidence on pharmacoutilization from a large real-world sample and from a centre for cognitive disturbances and dementia. European journal of clinical pharmacology. 2021;77(2):241-9.
16. Sampson EL, White N, Lord K, Leurent B, Vickerstaff V, Scott S, et al. Pain, agitation, and behavioural problems in people with dementia admitted to general hospital wards: a longitudinal cohort study. Pain. 2015;156(4):675-83.
17. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. Jama. 2005;294(15):1934-43.
18. Rajkumar AP, Ballard C, Fossey J, Orrell M, Moniz-Cook E, Woods RT, et al. Epidemiology of Pain in People With Dementia Living in Care Homes: Longitudinal Course, Prevalence, and Treatment Implications. Journal of the American Medical Directors Association. 2017;18(5):453. e1-.e6.
19. Husebo BS, Ballard C, Sandvik R, Nilsen OB, Aarsland D. Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomised clinical trial. BMJ (Clinical research ed). 2011;343:d4065.
20. Kales HC, Lyketsos CG, Miller EM, Ballard C. Management of behavioral and psychological symptoms in people with Alzheimer's disease: an international Delphi consensus. International psychogeriatrics. 2019;31(1):83-90.
21. Ballard CG, Gauthier S, Cummings JL, Brodaty H, Grossberg GT, Robert P, et al. Management of agitation and aggression associated with Alzheimer disease. Nature reviews Neurology. 2009;5(5):245-55.
22. Corbett A, Burns A, Ballard C. Don't use antipsychotics routinely to treat agitation and aggression in people with dementia. Bmj. 2014;349:g6420.
23. Ball EL, Owen-Booth B, Gray A, Shenkin SD, Hewitt J, McCleery J. Aromatherapy for dementia. The Cochrane database of systematic reviews. 2020;8(8):Cd003150.
24. Cooke B, Ernst E. Aromatherapy: a systematic review. The British journal of general practice : the journal of the Royal College of General Practitioners. 2000;50(455):493-6.
25. Dimitriou TD, Verykouki E, Papatriantafyllou J, Konsta A, Kazis D, Tsolaki M. Non-pharmacological interventions for agitation/aggressive behaviour in patients with dementia: a randomized controlled crossover trial. Functional neurology. 2018;33(3):143-7.
26. Dimitriou TD, Verykouki E, Papatriantafyllou J, Konsta A, Kazis D, Tsolaki M. Non-Pharmacological interventions for the anxiety in patients with dementia. A cross-over randomised controlled trial. Behavioural brain research. 2020;390:112617.
27. Fung JKK, Tsang HW. Management of behavioural and psychological symptoms of dementia by an aroma-massage with acupressure treatment protocol: A randomised clinical trial. Journal of clinical nursing. 2018;27(9-10):1812-25.
28. Kouzuki M, Kitao S, Kaju T, Urakami K. Evaluation of the effect of aroma oil as a bath salt on cognitive function. Psychogeriatrics : the official journal of the Japanese Psychogeriatric Society. 2020;20(2):163-71.
29. Mascherona I, Ferretti M, Soldini E, Biggiogero M, Maggioli C, Fontana PE. Essential oil therapy for the short-term treatment of behavioral and psychological symptoms of dementia: a monocentric randomized pilot study. Aging clinical and experimental research. 2021;33(8):2251-9.
30. Takahashi Y, Shindo S, Kanbayashi T, Takeshima M, Imanishi A, Mishima K. Examination of the influence of cedar fragrance on cognitive function and behavioral and psychological symptoms of dementia in Alzheimer type dementia. Neuropsychopharmacology reports. 2020;40(1):10-5.
31. Watson K, Hatcher D, Good A. A randomised controlled trial of Lavender (Lavandula Angustifolia) and Lemon Balm (Melissa Officinalis) essential oils for the treatment of agitated behaviour in older people with and without dementia. Complementary therapies in medicine. 2019;42:366-73.
32. Scuteri D, Rombolà L, Tridico L, Mizoguchi H, Watanabe C, Sakurada T, et al. Neuropharmacological properties of the essential oil of bergamot for the clinical management of pain-related BPSDs. Current medicinal chemistry. 2019;26(20):3764-74.
33. Long JM, Holtzman DM. Alzheimer Disease: An Update on Pathobiology and Treatment Strategies. Cell. 2019;179(2):312-39.
34. Finkel SI. Behavioral and psychologic symptoms of dementia. Clinics in geriatric medicine. 2003;19(4):799-824.
35. Huang YJ, Lin CH, Lane HY, Tsai GE. NMDA Neurotransmission Dysfunction in Behavioral and Psychological

Symptoms of Alzheimer's Disease. Current neuropharmacology. 2012;10(3):272-85.
36. Wise EA, Rosenberg PB, Lyketsos CG, Leoutsakos JM. Time course of neuropsychiatric symptoms and cognitive diagnosis in National Alzheimer's Coordinating Centers volunteers. Alzheimers Dement (Amst). 2019;11:333-9.
37. Vik-Mo AO, Giil LM, Ballard C, Aarsland D. Course of neuropsychiatric symptoms in dementia: 5-year longitudinal study. International journal of geriatric psychiatry. 2018;33(10):1361-9.
38. Lanctôt KL, Amatniek J, Ancoli-Israel S, Arnold SE, Ballard C, Cohen-Mansfield J, et al. Neuropsychiatric signs and symptoms of Alzheimer's disease: New treatment paradigms. Alzheimer's & Dementia: Translational Research & Clinical Interventions. 2017;3(3):440-9.
39. Cummings J. The Role of Neuropsychiatric Symptoms in Research Diagnostic Criteria for Neurodegenerative Diseases. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2021;29(4):375-83.
40. Ismail Z, Aguera-Ortiz L, Brodaty H, Cieslak A, Cummings J, Fischer CE, et al. The Mild Behavioral Impairment Checklist (MBI-C): A Rating Scale for Neuropsychiatric Symptoms in Pre-Dementia Populations. Journal of Alzheimer's disease : JAD. 2017;56(3):929-38.
41. Barnes DE, Alexopoulos GS, Lopez OL, Williamson JD, Yaffe K. Depressive symptoms, vascular disease, and mild cognitive impairment: findings from the Cardiovascular Health Study. Archives of general psychiatry. 2006;63(3):273-9.
42. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396(10248):413-46.
43. Sheikh F, Ismail Z, Mortby ME, Barber P, Cieslak A, Fischer K, et al. Prevalence of mild behavioral impairment in mild cognitive impairment and subjective cognitive decline, and its association with caregiver burden. International Psychogeriatrics. 2017;30(2):233-44.
44. Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. Jama. 2002;288(12):1475-83.
45. Modrego PJ, Ferrández J. Depression in patients with mild cognitive impairment increases the risk of developing dementia of Alzheimer type: a prospective cohort study. Archives of neurology. 2004;61(8):1290-3.
46. Aalten P, Verhey FRJ, Boziki M, Brugnolo A, Bullock R, Byrne EJ, et al. Consistency of Neuropsychiatric Syndromes across Dementias: Results from the European Alzheimer Disease Consortium. Dementia and geriatric cognitive disorders. 2008;25(1):1-8.
47. Savva GM, Zaccai J, Matthews FE, Davidson JE, McKeith I, Brayne C. Prevalence, correlates and course of behavioural and psychological symptoms of dementia in the population. The British journal of psychiatry : the journal of mental science. 2009;194(3):212-9.
48. Brodaty H, Connors MH, Xu J, Woodward M, Ames D. The course of neuropsychiatric symptoms in dementia: a 3-year longitudinal study. Journal of the American Medical Directors Association. 2015;16(5):380-7.
49. Forlenza OV, Diniz BS, Gattaz WF. Diagnosis and biomarkers of predementia in Alzheimer's disease. BMC Medicine. 2010;8(1):89.
50. Gordon BA, Blazey TM, Su Y, Hari-Raj A, Dincer A, Flores S, et al. Spatial patterns of neuroimaging biomarker change in individuals from families with autosomal dominant Alzheimer's disease: a longitudinal study. The Lancet Neurology. 2018;17(3):241-50.
51. Tynkkynen J, Chouraki V, van der Lee SJ, Hernesniemi J, Yang Q, Li S, et al. Association of branched-chain amino acids and other circulating metabolites with risk of incident dementia and Alzheimer's disease: A prospective study in eight cohorts. Alzheimer's & Dementia. 2018;14(6):723-33.
52. Ragneskog H, Gerdner LA, Josefsson K, Kihlgren M. Probable Reasons for Expressed Agitation in Persons with Dementia. Clinical Nursing Research. 1998;7(2):189-206.
53. Volicer L, Frijters DH, Van der Steen JT. Relationship between symptoms of depression and agitation in nursing home residents with dementia. International journal of geriatric psychiatry. 2012;27(7):749-54.
54. Rose KM, Beck C, Tsai P-F, Liem PH, Davila DG, Kleban M, et al. Sleep disturbances and nocturnal agitation behaviors in older adults with dementia. Sleep. 2011;34(6):779-86.
55. Lee D, Heo SH, Yoon SS, Chang DI, Lee S, Rhee HY, et al. Sleep disturbances and predictive factors in caregivers of patients with mild cognitive impairment and dementia. Journal of clinical neurology (Seoul, Korea). 2014;10(4):304-13.
56. Schuster BG, Kosar L, Kamrul R. Constipation in older adults: stepwise approach to keep things moving. Can Fam Physician. 2015;61(2):152-8.
57. Kales HC, Gitlin LN, Lyketsos CG, Detroit Expert Panel on A, Management of Neuropsychiatric Symptoms of D. Management of neuropsychiatric symptoms of dementia in clinical settings: recommendations from a multidisciplinary expert panel. Journal of the American Geriatrics Society. 2014;62(4):762-9.
58. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. Journal of the American Geriatrics Society. 2012; 60(4):616-31.
59. Tampi RR, Tampi DJ. Efficacy and tolerability of benzodiazepines for the treatment of behavioral and psychological symptoms of dementia: a systematic review of randomized controlled trials. American journal of Alzheimer's disease and other dementias. 2014;29(7):565-74.
60. Frederiksen KS, Waldemar G. Aggression, Agitation, Hyperactivity, and Irritability. In: Verdelho A, Gonçalves-Pereira

M, editors. Neuropsychiatric Symptoms of Cognitive Impairment and Dementia. Cham: Springer International Publishing; 2017. p. 199-236.
61. Kong E-H. Agitation in dementia: concept clarification. Journal of Advanced Nursing. 2005;52(5):526-36.
62. Bachman D, Rabins P. "Sundowning" and Other Temporally Associated Agitation States in Dementia Patients. Annual Review of Medicine. 2006;57(1):499-511.
63. Carrarini C, Russo M, Dono F, Barbone F, Rispoli MG, Ferri L, et al. Agitation and Dementia: Prevention and Treatment Strategies in Acute and Chronic Conditions. Frontiers in Neurology. 2021;12.
64. Petersen JD, Wehberg S, Packness A, Svensson NH, Hyldig N, Raunsgaard S, et al. Association of Socioeconomic Status With Dementia Diagnosis Among Older Adults in Denmark. JAMA network open. 2021;4(5):e2110432.
65. Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. The Lancet Neurology. 2016;15(5):455-532.
66. Gagliese L, Melzack R. Chronic pain in elderly people. Pain. 1997;70(1):3-14.
67. Fitzcharles MA, Lussier D, Shir Y. Management of chronic arthritis pain in the elderly. Drugs & aging. 2010; 27(6):471-90.
68. Wang W, Li X, Ren Y. Correlation Analysis and Intervention Study on Disturbance of Lipid Metabolism and Diabetic Peripheral Neuropathy. Computational and mathematical methods in medicine. 2022;2022:2579692.
69. John AR, Canaday DH. Herpes Zoster in the Older Adult. Infect Dis Clin North Am. 2017;31(4):811-26.
70. Ahuja D, Choudhary N, Kumar V, Gupta N, Jee Bharati S. Managing breakthrough pain for advanced malignancy in elderly patients: A real challenge. Journal of opioid management. 2020;16(3):219-22.
71. Corbett A, Husebo B, Malcangio M, Staniland A, Cohen-Mansfield J, Aarsland D, et al. Assessment and treatment of pain in people with dementia. Nature reviews Neurology. 2012;8(5):264-74.
72. Sampson EL, White N, Lord K, Leurent B, Vickerstaff V, Scott S, et al. Pain, agitation, and behavioural problems in people with dementia admitted to general hospital wards: a longitudinal cohort study. Pain. 2015;156(4).
73. Atee M, Morris T, Macfarlane S, Cunningham C. Pain in Dementia: Prevalence and Association With Neuropsychiatric Behaviors. Journal of Pain and Symptom Management. 2021;61(6):1215-26.
74. Rose VL. Guidelines from the American Geriatric Society target management of chronic pain in older persons. American family physician. 1998;58(5):1213-4, 7.
75. The management of persistent pain in older persons. J Am Geriatr Soc. 2002;50(6 Suppl):S205-24.
76. Franceschi M, Scarcelli C, Niro V, Seripa D, Pazienza AM, Pepe G, et al. Prevalence, clinical features and avoidability of adverse drug reactions as cause of admission to a geriatric unit: a prospective study of 1756 patients. Drug safety. 2008;31(6):545-56.
77. Lanza F, Rack MF, Doucette M, Ekholm B, Goldlust B, Wilson R. An endoscopic comparison of the gastroduodenal injury seen with salsalate and naproxen. The Journal of rheumatology. 1989;16(12):1570-4.
78. Ruschitzka F, Borer JS, Krum H, Flammer AJ, Yeomans ND, Libby P, et al. Differential blood pressure effects of ibuprofen, naproxen, and celecoxib in patients with arthritis: the PRECISION-ABPM (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen Ambulatory Blood Pressure Measurement) Trial. European Heart Journal. 2017;38(44):3282-92.
79. Zhang Q, Bal-dit-Sollier C, Drouet L, Simoneau G, Alvarez JC, Pruvot S, et al. Interaction between acetaminophen and warfarin in adults receiving long-term oral anticoagulants: a randomized controlled trial. European journal of clinical pharmacology. 2011;67(3):309-14.
80. Sandvik RK, Selbaek G, Seifert R, Aarsland D, Ballard C, Corbett A, et al. Impact of a stepwise protocol for treating pain on pain intensity in nursing home patients with dementia: a cluster randomized trial. European journal of pain. 2014;18(10):1490-500.
81. Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S. Duloxetine vs. placebo in patients with painful diabetic neuropathy. Pain. 2005;116(1-2):109-18.
82. Sindrup SH, Otto M, Finnerup NB, Jensen TS. Antidepressants in the treatment of neuropathic pain. Basic & clinical pharmacology & toxicology. 2005;96(6):399-409.
83. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016. MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports. 2016;65(1):1-49.
84. Allan L, Hays H, Jensen NH, de Waroux BL, Bolt M, Donald R, et al. Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. Bmj. 2001;322(7295):1154-8.
85. Fine PG. Chronic pain management in older adults: special considerations. J Pain Symptom Manage. 2009;38 (2 Suppl):S4-s14.
86. Ballard C, Corbett A. Agitation and aggression in people with Alzheimer's disease. Current opinion in psychiatry. 2013;26(3):252-9.
87. Achterberg WP, Pieper MJ, van Dalen-Kok AH, de Waal MW, Husebo BS, Lautenbacher S, et al. Pain management in patients with dementia. Clinical interventions in aging. 2013;8:1471-82.
88. Achterberg WP, Erdal A, Husebo BS, Kunz M, Lautenbacher S. Are Chronic Pain Patients with Dementia Being Undermedicated? Journal of pain research. 2021;14:431-9.
89. Bayer A, Tadd W. Unjustified exclusion of elderly people from studies submitted to research ethics committee for approval: descriptive study. Bmj. 2000;321(7267):992-3.

90. Scuteri D, Adornetto A, Rombolà L, Naturale MD, De Francesco AE, Esposito S, et al. Pattern of triptans use: a retrospective prescription study in Calabria, Italy. Neural regeneration research. 2020;15(7):1340-3.
91. Scuteri D, Corasaniti MT, Tonin P, Bagetta G. Eptinezumab for the treatment of migraine. Drugs of today. 2019;55(11):695-703.
92. Scuteri D, Corasaniti MT, Tonin P, Nicotera P, Bagetta G. Role of CGRP pathway polymorphisms in migraine: a systematic review and impact on CGRP mAbs migraine therapy. J Headache Pain. 2021;22(1):87.
93. Ballard C, Howard R. Neuroleptic drugs in dementia: benefits and harm. Nature reviews Neuroscience. 2006; 7(6):492-500.
94. Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2006;14(3):191-210.
95. Scuteri D, Morrone LA, Rombola L, Avato PR, Bilia AR, Corasaniti MT, et al. Aromatherapy and Aromatic Plants for the Treatment of Behavioural and Psychological Symptoms of Dementia in Patients with Alzheimer's Disease: Clinical Evidence and Possible Mechanisms. Evidence-based complementary and alternative medicine : eCAM. 2017;2017:9416305.
96. Forrester LT, Maayan N, Orrell M, Spector AE, Buchan LD, Soares-Weiser K. Aromatherapy for dementia. The Cochrane database of systematic reviews. 2014(2):Cd003150.
97. Rombolà L, Scuteri D, Marilisa S, Watanabe C, Morrone LA, Bagetta G, et al. Pharmacokinetic Interactions between Herbal Medicines and Drugs: Their Mechanisms and Clinical Relevance. Life (Basel, Switzerland). 2020;10(7).
98. Scuteri D, Guida F, Boccella S, Luongo L, Maione S, Tonin P, et al. NAbiximols Clinical Translation To the treatment of Pain and Agitation In Severe Dementia (NACTOPAISD): Clinical trial protocol. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2022;153:113488.
99. Amantea D, Spagnuolo P, Bari M, Fezza F, Mazzei C, Tassorelli C, et al. Modulation of the endocannabinoid system by focal brain ischemia in the rat is involved in neuroprotection afforded by 17beta-estradiol. The FEBS journal. 2007;274(17):4464-775.
100. Wu GA, Terol J, Ibanez V, López-García A, Pérez-Román E, Borredá C, et al. Genomics of the origin and evolution of Citrus. Nature. 2018;554(7692):311-6.
101. Maruca G, Laghetti G, Mafrica R, Turiano D, Hammer K. The Fascinating History of Bergamot (Citrus Bergamia Risso & Poiteau), the Exclusive Essence of Calabria: A Review. JESE-A. 2017;6.
102. Valussi M, Donelli D, Firenzuoli F, Antonelli M. Bergamot Oil: Botany, Production, Pharmacology. Encyclopedia. 2021;1(1):152-76.
103. Stato IPeZd. Farmacopea Ufficiale Italiana. Droghe Vegetali e Preparazioni (IX Edizione). 1991:75.
104. Mondello L, Stagno d'Alcontres I, Del Duce R, Crispo F. On the genuineness of citrus essential oils. Part XL. The composition of the coumarins and psoralens of Calabrian bergamot essential oil (Citrus bergamia Risso). Flavour and Fragrance Journal. 1993;8(1):17-24.
105. Sakurada T, Kuwahata H, Katsuyama S, Komatsu T, Morrone LA, Corasaniti MT, et al. Chapter 18 Intraplantar Injection Of Bergamot Essential Oil Into The Mouse Hindpaw. Effects On Capsaicin-Induced Nociceptive Behaviors. International review of neurobiology2009. p. 237-48.
106. Kuwahata H, Komatsu T, Katsuyama S, Corasaniti MT, Bagetta G, Sakurada S, et al. Peripherally injected linalool and bergamot essential oil attenuate mechanical allodynia via inhibiting spinal ERK phosphorylation. Pharmacology Biochemistry and Behavior. 2013;103(4):735-41.
107. Hamamura K, Katsuyama S, Komatsu T, Scuteri D, Bagetta G, Aritake K, et al. Behavioral Effects of Continuously Administered Bergamot Essential Oil on Mice With Partial Sciatic Nerve Ligation. Frontiers in pharmacology. 2020;11:1310.
108. Hooijmans CR, Rovers MM, de Vries RBM, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Medical Research Methodology. 2014;14(1):43.
109. Macleod MR, O'Collins T, Howells DW, Donnan GA. Pooling of Animal Experimental Data Reveals Influence of Study Design and Publication Bias. Stroke. 2004; 35(5):1203-8.
110. Rombolà L, Tridico L, Scuteri D, Sakurada T, Sakurada S, Mizoguchi H, et al. Bergamot essential oil attenuates anxiety-like behaviour in rats. Molecules. 2017;22(4).
111. Rombolà L, Scuteri D, Watanabe C, Sakurada S, Hamamura K, Sakurada T, et al. Role of 5-HT1A Receptor in the Anxiolytic-Relaxant Effects of Bergamot Essential Oil in Rodent. International journal of molecular sciences. 2020;21(7).
112. Zaynoun ST, Johnson BE, Frain-Bell W. A study of oil of bergamot and its importance as a phototoxic agent. British Journal of Dermatology. 1977;96(5):475-82.
113. Scuteri D, Cassano R, Trombino S, Russo R, Mizoguchi H, Watanabe C, et al. Development and Translation of NanoBEO, a Nanotechnology-Based Delivery System of Bergamot Essential Oil Deprived of Furocumarins, in the Control of Agitation in Severe Dementia. Pharmaceutics. 2021;13(3).
114. Scuteri D, Rombolà L, Crudo M, Watanabe C, Mizoguchi H, Sakurada S, et al. Preclinical Characterization of Antinociceptive Effect of Bergamot Essential Oil and of Its Fractions for Rational Translation in Complementary Therapy. Pharmaceutics. 2022;14(2).
115. Scuteri D, Rombolà L, Crudo M, Watanabe C, Mizoguchi H, Sakurada S, et al. Translational Value of the Transdermal Administration of Bergamot Essential Oil and of Its Fractions. Pharmaceutics. 2022;14(5).

116. Scuteri D, Rombolà L, Hayashi T, Watanabe C, Sakurada S, Hamamura K, et al. Analgesic Characteristics of NanoBEO Released by an Airless Dispenser for the Control of Agitation in Severe Dementia. Molecules. 2022;27(15).
117. Scuteri D, Sandrini G, Tamburin S, Corasaniti MT, Nicotera P, Tonin P, et al. Bergamot rehabilitation AgaINst agitation in dementia (BRAINAID): Study protocol for a randomized, double-blind, placebo-controlled trial to assess the efficacy of furocoumarin-free bergamot loaded in a nanotechnology-based delivery system of the essential oil in the treatment of agitation in elderly affected by severe dementia. Phytotherapy research : PTR. 2021;35(10):5333-8.
118. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. Bmj. 2010;340:c869.
119. Scuteri D, Contrada M, Loria T, Sturino D, Cerasa A, Tonin P, et al. Pain and agitation treatment in severe dementia patients: The need for Italian Mobilization–Observation–Behavior–Intensity–Dementia (I-MOBID2) pain scale translation, adaptation and validation with psychometric testing. Biomedicine & Pharmacotherapy. 2022;150:113013.
120. Hadjistavropoulos T, Herr K, Turk DC, Fine PG, Dworkin RH, Helme R, et al. An interdisciplinary expert consensus statement on assessment of pain in older persons. The Clinical journal of pain. 2007;23(1 Suppl):S1-43.
121. Husebo BS, Strand LI, Moe-Nilssen R, Husebo SB, Ljunggren AE. Pain in older persons with severe dementia. Psychometric properties of the Mobilization-Observation-Behaviour-Intensity-Dementia (MOBID-2) Pain Scale in a clinical setting. Scandinavian journal of caring sciences. 2010;24(2):380-91.

Correspondence:
Damiana Scuteri
E-mail: damiana.scuteri@unical.it
Luigi Antonio Morrone
E-mail: luigi.morrone@unical.it
Pharmacotechnology Documentation and Transfer Unit, Preclinical and Translational Pharmacology, Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, 87036 Rende, Italy.
Tel./Fax: +390984/493462; +390984/493054

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Metafore concettuali e framing in linguistica cognitiva

Serena Coschignano
Università degli Studi di Pavia. Dipartimento di Studi Umanistici, Sezione di Linguistica Teorica e Applicata, Pavia.

Riassunto: L'articolo illustra i punti fondamentali della Teoria della Metafora Concettuale e del framing. In particolare, si propone una lettura di alcune espressioni linguistiche d'uso quotidiano la cui natura metaforica può non essere immediatamente riconoscibile. Si discutono le implicazioni del framing di diversi campi dell'esperienza attraverso il linguaggio bellico: dalle discussioni, al rapporto paziente-malattia, alla situazione emergenziale causata dalla pandemia da Covid-19. Infine, si mostra come il paradigma teorico della Linguistica Cognitiva abbia trovato applicazione nell'analisi critica del discorso pubblico, commentando esempi di rappresentazione del fenomeno migratorio nei titoli della stampa italiana.

Parole chiave: teoria della metafora concettuale, framing, linguistica cognitiva, analisi critica del discorso

Conceptual metaphors and framing in Cognitive Linguistics
Abstract. This paper illustrates the essential aspects of Conceptual Metaphor Theory and framing. In particular, it presents an analysis of every-day linguistic expressions whose metaphorical nature may not be immediately recognizable. Furthermore, it discusses the implications of the use of "war" metaphors for the framing of different domains of experience: discussions, the patient-disease relationship, and the emergency situation caused by the Covid-19 pandemic. Finally, it shows how the theoretical paradigm of Cognitive Linguistics has been applied to the critical analysis of public discourse: this is illustrated with examples of the representation of the migrations in Italian press headlines.

Key words: conceptual metaphor theory, framing, cognitive linguistics, critical discourse analysis

Introduzione

Secondo la Teoria della Metafora Concettuale (TMC), il pensiero metaforico è un meccanismo fondamentale per la capacità umana di concepire la realtà e gli eventi. Tale teoria è stata sviluppata a cavallo tra gli studi linguistici e quelli filosofici a partire dagli anni Ottanta (1), ma si inserisce in una tradizione che ha radici già nel pensiero aristotelico (2) ed è oggi supportata da evidenze empiriche nel campo delle neuroscienze (3,4).[1] In Linguistica Cognitiva (LC), quando si parla di metafora si intende un fatto primariamente cognitivo e solo secondariamente linguistico: il linguaggio è il mezzo che permette di organizzare ed esprimere i concetti elaborati nel corso della nostra esperienza del mondo, la cui comprensione è guidata, appunto, da una modalità di pensiero di tipo metaforico. Il linguaggio, dunque, fornisce un punto di accesso alla struttura che i concetti assumono nella nostra mente.

Nelle sezioni che seguono si illustreranno i punti cardine della TMC avvalendosi di espressioni tratte dal linguaggio quotidiano; si introdurrà poi il concetto di framing (5) attraverso l'analisi di metafore belliche in uso in diversi campi dell'esperienza; infine,

1 - Per una panoramica sull'evoluzione del pensiero filosofico, linguistico e psicologico attorno alla metafora, si veda (8).

si presenterà un recente filone di studi che applica i costrutti teorici della LC all'analisi critica del discorso (6,7).

L'associazione metaforica tra esperienze fisiche e psicologiche: l'embodied cognition, o cognizione incarnata

Prendiamo come primo esempio l'uso dei termini *caldo* e *freddo*.[2] Oltre a impiegare questi aggettivi per descrivere la temperatura atmosferica ("oggi fa caldo"), la temperatura di un oggetto ("la bottiglia è fredda") o una sensazione interiore ("ho molto caldo"), i due termini trovano impiego in un ampio repertorio di espressioni metaforiche, all'interno delle quali assumono significati diversi. Ad esempio, possiamo descrivere una persona come un *freddo calcolatore*, così come possiamo dire di qualcuno che ha un *carattere freddo*, o ancora di avere ricevuto un *saluto freddo*. Al contrario, possiamo affermare che in una certa circostanza ci è stata riservata una *calda accoglienza*, o che qualcuno è dotato di una *voce calda*, o, ancora, di aver ricevuto un *abbraccio caldo* riferendoci, nell'ultimo caso, non al calore corporeo che abbiamo percepito nell'esperienza dell'abbraccio, ma piuttosto al grado di coinvolgimento e prossimità sociale che abbiamo provato nei confronti della persona con la quale abbiamo condiviso tale esperienza.

Le espressioni precedenti, usate per descrivere tratti di personalità e comportamenti sociali, traggono in effetti origine da esperienze corporee: alla base vi è l'associazione di una sensazione di calore con l'esperienza di vicinanza fisica, quindi letterale, a un altro individuo; attraverso il meccanismo di pensiero metaforico, poi, siamo arrivati a trasferire il concetto di vicinanza fisica su quello di vicinanza sociale, emotiva, empatica (9). Gli stessi termini compaiono anche in espressioni che non suggeriscono immediatamente la partecipazione di altri individui alla nostra esperienza, come *provare una sensazione calda* (intendendo, con ciò, PIACEVOLE), oppure percepire un'*atmosfera fredda* (che ci arreca DISAGIO). L'uso di termini di temperatura in questi contesti può essere spiegato a partire da diverse direttrici. Seguendo la Conflation Theory (10), ad esempio, l'associazione CALDO-PIACEVOLE / FREDDO-SPIACEVOLE affonderebbe le sue radici nell'esperienza corporea della prima infanzia: quando un neonato viene cullato, esperisce una sensazione di calore (per la vicinanza fisica con la persona che lo tiene tra le braccia) insieme a quella piacevole e confortante di essere protetto. I due concetti, dunque, si sarebbero legati nella mente dell'infante prima che questo sia in grado di discernere tra sensazioni fisiche e psicologiche.[3] E, in effetti, in Semantica Cognitiva si parla di embodied cognition (traducibile come "cognizione incarnata"), considerando la mente e il pensiero come imprescindibilmente legati all'esperienza corporea. Non solo: sarebbe proprio l'esperienza corporea, in quanto diretta, a guidare l'elaborazione di concetti via via più complessi e astratti (11,12).

L'elaborazione di concetti guidata da configurazioni strutturali già note

Il pensiero metaforico, tuttavia, non si limita alla sola associazione tra concetti che ci si presentano contemporaneamente. Secondo la TMC, infatti, esso permea la nostra interazione quotidiana con la realtà. Ogni qualvolta un individuo entra in contatto con una nuova esperienza, sarà portato a tentare di incasellarla nelle categorie (o "domini") concettuali di cui ha già fatto esperienza e che già comprende. Lo stesso avviene per l'elaborazione di concetti complessi o astratti, che vengono interpretati sfruttando la struttura interna di domini di cui si ha esperienza diretta. Ad esempio, nella frase "Mi *hai dato* una buona idea" l'uso del verbo *dare* ci suggerisce che le idee siano metaforicamente concepite come degli OGGETTI, al pari dei quali possono essere *date*, *scambiate*, o anche *rubate* (1).

2 - Nel corso dell'articolo, si userà il *corsivo* per evidenziare i termini che evocano i domini concettuali di volta in volta discussi, che saranno invece segnalati in MAIUSCOLETTO.

3 - Secondo un'altra interpretazione, che non si propone necessariamente come alternativa alla prima, saremmo portati a pensare a una sensazione spiacevole come *fredda* per via dell'abbassamento della temperatura corporea che si verifica quando ci troviamo in uno stato di paura (14). Va da sé, infine, che l'associazione tra calore e piacevolezza non trova riscontro nel caso di temperature estreme (15,9).

Si noti che la buona riuscita di un'associazione metaforica non richiede che il dominio di partenza (p.es., OGGETTO) e quello di arrivo (p.es., IDEA) siano totalmente sovrapponibili. Prendiamo come esempio un'altra espressione tratta dal linguaggio quotidiano. È certamente possibile pensare alle *gambe del tavolo* senza bisogno di processare consapevolmente la natura metaforica del concetto. È infatti intuitivo pensare agli elementi che sostengono il ripiano orizzontale di un tavolo come a delle *gambe*, in quanto queste condividono alcune caratteristiche strutturali con le gambe umane, delle quali abbiamo una diretta esperienza: entrambi i tipi di elementi hanno una struttura verticale, una forma longilinea e assolvono a una funzione di sostegno nelle rispettive configurazioni, posizionandosi alla loro base. Se la condivisione di caratteristiche strutturali è sufficiente per rendere possibile una proiezione metaforica del dominio GAMBE su quello di TAVOLO, è però anche evidente che i due elementi non sono totalmente sovrapponibili: le *gambe* umane assolvono anche a una funzione di mobilità della struttura che sostengono, mentre lo stesso non vale per le *gambe del tavolo*. E tuttavia, se ci venisse mostrato uno scenario, ad esempio in un filmato d'animazione, nel quale un tavolo cominciasse a muoversi camminando, noi non avremmo alcun problema a interpretare ciò che stiamo osservando: anche se la mobilità non rientra tra le aree del dominio GAMBE necessarie all'elaborazione della metafora GLI ELEMENTI CHE SOSTENGONO UN TAVOLO SONO GAMBE, tale proprietà, che è parte della struttura del dominio di partenza, diventa all'occorrenza disponibile anche per il dominio di arrivo. Lo stesso si applica a concetti molto più complessi e/o distanti dall'esperienza quotidiana, la cui elaborazione viene guidata, come in questo caso, da domini più concreti.

L'uso di schemi mentali noti per l'interpretazione di nuove esperienze avviene nella maggior parte dei casi in automatico e a livello inconscio, senza richiedere un elevato sforzo cognitivo: è questa una modalità di pensiero di tipo associativo, con un costo cognitivo inferiore rispetto al cosiddetto pensiero analitico (13). Se il pensiero associativo è vitale per l'economicità con cui ci permette di muoverci nel mondo, esso ci espone anche a possibili fallacie interpretative. Come si è visto, infatti, quando usiamo un certo dominio dell'esperienza per comprenderne un altro proiettiamo sul secondo l'intera struttura del primo, comprese le sue parti non immediatamente disponibili. Non solo: selezionare (anche in modo inconsapevole) un dominio come base per l'interpretazione di un'esperienza ha la conseguenza di metterne in luce alcuni aspetti e lasciarne in ombra altri. Nella sezione successiva si presenteranno alcuni casi in cui la selezione di una tra più cornici interpretative possibili guida la nostra esperienza della realtà arrivando a produrre ricadute di ordine pratico.

Il framing attraverso il dominio concettuale del CONFLITTO

Quando si usa la struttura di un concetto per interpretarne un altro, si compie (inconsapevolmente) un'operazione di selezione tra diverse alternative: ogni ambito dell'esperienza si presterebbe ad essere interpretato attraverso più domini di partenza, che possono differire anche sensibilmente tra loro, e che possono essere sovrapponibili a un altro concetto sulla base di elementi diversi. Pensiamo al linguaggio usato per descrivere ciò che avviene durante una discussione: è possibile immaginare che una delle due parti abbia presentato delle *richieste indifendibili* e che la controparte abbia *attaccato ogni punto debole* dell'argomentazione *avversaria*, adottando una *strategia* vincente che ha *colpito nel segno* e portato alla *vittoria*. In alternativa, potremmo pensare a come entrambe le parti *si siano spese molto* per arrivare a un accordo, *venendosi incontro* sulle rispettive *posizioni* fino ad arrivare a un *punto comune* (si noti anche che lo stesso termine *parti* riflette una concezione metaforica della relazione reciproca tra i soggetti coinvolti nell'azione). Ciascuno dei due modi per descrivere una discussione ne pone in evidenza alcuni aspetti e ne lascia altri sullo sfondo: nel primo caso, se ne sottolinea la natura conflittuale; nel secondo, quella cooperativa. Nel linguaggio quotidiano, però, è molto più comune incontrare espressioni del primo tipo che non del secondo. Anche se non ne siamo (del tutto) consapevoli, il modo in cui ne parliamo convenzionalmente suggerisce che la visione di una DISCUSSIONE come CONFLITTO sia molto più radicata nel nostro immaginario rispetto a quella di ATTO COOPERATIVO. Questo tipo di concezione si riflette sul modo stesso in cui "viviamo" una discussione (1).

Mantenendo lo stesso dominio di partenza, mostriamo le implicazioni della costruzione metaforica di un'esperienza in un contesto diverso. Pensiamo a un'espressione come *combattere il cancro*: sovrapponendo il dominio concettuale del CONFLITTO – o, più precisamente, della LOTTA o della BATTAGLIA – a quello del CANCRO, si delinea uno scenario in cui i PAZIENTI diventano GUERRIERI impegnati in una *battaglia* per *sconfiggere* un *nemico* e che potrebbero risultare *vincitori* o *vinti*. Una concettualizzazione del cancro nei termini di una battaglia può influire negativamente sui pazienti, accrescendo la loro sensazione di vulnerabilità, di timore per una minaccia incombente e di fallimento personale nel caso in cui la malattia si rivelasse incurabile (16,17,18). Un altro dominio in uso per elaborare lo stesso concetto è quello del VIAGGIO: in questo caso, diremmo che i pazienti stanno affrontando un *percorso di cura*, con i loro cari ad *accompagnarli* in un difficile *cammino*[4]. È vero, però, che il ricorso al dominio del CONFLITTO in campo medico non è nuovo (lo stesso termine *debellare*, di origine latina, significa letteralmente "terminare la guerra, sconfiggere") e che sottrarsi a una cornice interpretativa consolidata richiede uno sforzo sia sul piano linguistico, sia su quello cognitivo (19).

La situazione di emergenza causata dalla pandemia da Covid-19 ha visto un'estensione della portata della metafora bellica, che dalla relazione malattia-paziente è arrivata a delineare quella malattia-nazione. La narrazione prevalente, portata avanti da diversi leader a livello mondiale, ha visto medici e infermieri tramutarsi in *combattenti*, impegnati *in prima linea* contro un *nemico* comune dal quale è diventato necessario *difendersi*. In questo caso è ancora più evidente come la metafora LA PANDEMIA DA COVID-19 È UNA GUERRA non si manifesti solo a livello linguistico, ma anche, appunto, concettuale: come ci si aspetterebbe in un contesto guerresco, soprattutto nelle prime fasi della pandemia, in Italia abbiamo assistito alla diffusione mediatica del *bollettino* giornaliero della Protezione Civile e le nuove misure governative erano annunciate di sera e messe in atto repentinamente. Anche in questo contesto è stata da più parti sottolineata la problematicità di una narrazione in termini bellici. Ad esempio, si è fatto leva su una dimensione emotiva, catalizzando l'attenzione mediatica sulle imprese straordinarie dei medici-eroi e lasciando sullo sfondo il tema dei problemi strutturali preesistenti nel sistema sanitario. Il linguaggio guerresco ha contribuito ad alimentare un clima di tensione che ha aperto la strada a scenari preoccupanti, come l'accentramento (momentaneo) di potere nelle mani del primo ministro ungherese (20).

In questa sezione si è visto come l'impiego di un dominio dell'esperienza per l'interpretazione di un altro trasferisca sul secondo anche implicazioni meno salienti del primo. Non solo: soprattutto con l'ultimo esempio, si è mostrato che ragionare nell'ottica di un certo dominio induce ad adeguare i propri comportamenti all'intera sfera concettuale evocata. Qualsiasi concetto, infatti, non viene interpretato in isolamento, ma sulla base di una struttura più ampia di concetti con i quali è collegato. È questo uno dei punti fondanti della Semantica dei Frame (5): il termine frame ("cornice") indica un sistema di concetti che vengono resi disponibili non appena uno di essi è attivato – ad esempio, da un'espressione linguistica. Il framing si fonda sullo stesso meccanismo già descritto per il pensiero metaforico e consiste nell'inquadrare un'esperienza all'interno di un intero schema mentale che si è già acquisito. In quanto reti di concetti connessi tra loro, i frame costituiscono modelli narrativi e interpretativi della realtà. Fare framing, dunque, significa usare un linguaggio che riflette una certa visione del mondo, imponendo indirettamente all'interlocutore una certa narrazione del reale tra quelle possibili (19). Come già anticipato, però, domini e cornici interpretative non sono sempre selezionati in modo intenzionale. Nell'ultima sezione si presenterà una prospettiva di ricerca che adotta i costrutti teorici della LC per rendere espliciti presupposti e implicazioni ideologici celati nel discorso pubblico.

La Linguistica Cognitiva come paradigma per l'analisi critica del discorso

In anni recenti, i costrutti teorici della LC sono sempre più spesso applicati all'analisi critica del

4 - È stato però sottolineato che alcuni pazienti provano un senso di orgoglio nell'affrontare l'esperienza della malattia come una lotta e invitano gli operatori sanitari a non escludere a priori l'uso di questo tipo di metafore, evidenziando anche potenziali aspetti problematici legati alla metafora del viaggio (16).

discorso mediatico e politico, con particolare attenzione alla narrazione di temi di rilevanza sociale (6,7). L'obiettivo di questi studi è quello di fare luce su come il discorso pubblico contribuisca a mantenere in essere sistemi di diseguaglianza sociale, che sono implicitamente riprodotti attraverso il linguaggio. Analizzando le cornici discorsive, ad esempio, è possibile ricostruire le posizioni ideologiche (anche inconsapevoli) dei parlanti (21).

Vediamo l'esempio di alcune espressioni d'uso comune nei titoli di giornale degli ultimi anni: ampio spazio è stato dedicato al racconto delle soluzioni adottate per *arginare* le *ondate* di profughi e per *gestirli* una volta arrivati e si è sentito spesso parlare dei criteri per la loro *redistribuzione* sul territorio attraverso un sistema di *quote*. In questi casi, il framing del fenomeno migratorio fa uso di domini concettuali nei quali profughi, migranti e rifugiati assumono i contorni di MASSE D'ACQUA, di OGGETTI, o di generiche ENTITÀ INANIMATE razionabili numericamente, nascondendone la natura umana ed individuale (22). Non si tratta di una narrazione esplicitamente disumanizzante, come quella che si può trovare nei resoconti di testate che non fanno mistero della propria posizione ideologica sulla questione migratoria: leggendo un testo apertamente discriminatorio, i fruitori di notizie sono facilmente in grado di identificarlo come tale (e, eventualmente, di rigettarlo). Di contro, si è osservato che non è altrettanto immediato realizzare di stare adottando una cornice interpretativa discriminatoria quando questa è presentata con toni pacati (7). Inoltre, quando una certa narrazione si consolida al punto tale da entrare a far parte del linguaggio comune, diventa ancora più difficile scorgerne la matrice ideologica e riconoscerne l'eventuale origine metaforica. Questa difficoltà interessa tanto i ricettori delle notizie, quanto i loro produttori: escludendo i discorsi apertamente discriminatori, gli stessi frame oggettificanti si possono trovare in quotidiani altrimenti distanti per posizionamento ideologico (23).

Conclusioni

In questo contributo si sono approfonditi alcuni costrutti teorici della LC, delineati attraverso l'analisi di espressioni linguistiche di uso comune. È stata evidenziata la natura primariamente concettuale (e solo secondariamente linguistica) delle metafore e si è mostrato come l'uso di cornici interpretative del reale possa realizzarsi in modo inconsapevole per i parlanti. Si sono commentate le implicazioni potenzialmente problematiche della concezione delle DISCUSSIONI, del CANCRO e della PANDEMIA DA COVID-19 entro la cornice interpretativa della GUERRA. Infine, si è mostrata l'applicazione del paradigma teorico della Linguistica Cognitiva agli studi di analisi critica del discorso pubblico, presentando esempi di raffigurazione del fenomeno migratorio tratti da titoli di quotidiani italiani, che mostrano un framing oggettificante per gli attori sociali rappresentati.

Bibliografia

1. Lakoff G, Johnson M. Metaphors we live by. Chicago: The University of Chicago Press 1980.
2. Eco U. Aspetti conoscitivi della metafora in Aristotele. Doctor Virtualis 2004; 3.
3. Narayanan SK. Knowledge-based Action Representations for Metaphor and Aspect. Berkeley: University of California PhD Thesis 1997.
4. Kövecses Z. Some recent issues in conceptual metaphor theory. In: Prandi M. & Rossi M. eds. Researching Metaphors: Towards a Comprehensive Account. New York: Routledge 2022.
5. Fillmore C. Frame semantics. In: Geeraerts D. ed. Cognitive Linguistics: Basic Readings. Berlin, New York: De Gruyter Mouton 2008[1982]; 373-400.
6. Hart C. Cognitive Linguistics and Critical Discourse Analysis. In: Dabrowska E. & Divjak D. eds. Handbook of Cognitive Linguistics. Berlin: De Gruyter 2015; 322-345.
7. Hart C. Animals vs. armies: Resistance to extreme metaphors in anti-immigration discourse. Journal of Language and Politics 2021; 20(2): 226-253.
8. La Mura I. La costruzione di senso e lo scambio di risorse simboliche: Metafore, frames e comunicazione. Università di Firenze (tesi di Dottorato) 2010.
9. Coschignano S. The semantic network of temperature: Non-sensory domains accessed with metaphorical extensions of the Italian adjectives caldo and freddo. Review of Cognitive Linguistics 2021; 19(1): 232-258.
10. Johnson C. Metaphor vs. conflation in the acquisition of polysemy: The case of see. In: Hiraga M.K., Sinha C. & Wilcox S. eds. Cultural, typological and psychological issues in Cognitive Linguistics. Amsterdam & Philadelphia: John Benjamins 1997; 155-169.
11. Johnson M. The body in the mind: The bodily basis of meaning, imagination, and reason. Chicago: University of Chicago Press 1987.

12. Rohrer T. Embodiment and experientialism. In Geeraerts D. & Cuyckens H. eds. The Oxford handbook of Cognitive Linguistics. Oxford: Oxford University Press 2007; 25-47.
13. Evans JStBT. Hypothetical Thinking. Dual Processes in Reasoning and Judgement. Hove: Psychology Press 2007.
14. Apresjan V. Emotion metaphors and cross-linguistic conceptualization of emotions. Cuadernos de filología inglesa 1997; 612: 179-195.
15. Luraghi S. Asymmetries in Italian temperature terminology. In: Koptjevskaja-Tamm M. ed. Linguistics of temperature. Amsterdam & Philadelphia: John Benjamins 2015; 333-353.
16. Semino E, Demjén Z, Demmen J, et al. The online use of Violence and Journey metaphors by patients with cancer, as compared with health professionals: a mixed methods study. BMJ Supportive & Palliative Care 2015; 7(1): 60-66.
17. Hendricks RK, Demjén Z, Semino E, Boroditsky L. Emotional implications of metaphor: consequences of metaphor framing for mindset about cancer. Metaphor Symbol 2018; 33(4): 267-279.
18. Wackers DYM, Plug HJ, Steen GJ. "For crying out loud, don't call me a warrior": Standpoints of resistance against violence metaphors for cancer. Journal of Pragmatics 2021; 174: 68-77.
19. Lakoff G. Don't think of an elephant!. White River Junction, VT: Chelsea Green Pub 2004.
20. Luraghi S. Metafora. Fondazione Feltrinelli 2021. https://fondazionefeltrinelli.it/metafora/ (accesso 10 ottobre 2022).
21. Fairclough N. Language and Power. London: Longman 1989.
22. Coschignano S, Zanchi C. Linguistic Means to Discursively Construct Dehumanization. In: Deckert M., Pęzik P. & Zago R. eds. Language, Expressivity and Cognition. London: Bloomsbury (in corso di stampa); 55-82.
23. Zanchi C. Dei frame e del (ri)produrre inconsapevolmente discorsi ingiusti. Linguisticamente 2022. https://www.linguisticamente.org/dei-frame-e-del-riprodurre-inconsapevolmente-discorsi-ingiusti/ (accesso 10 ottobre 2022).

Correspondence:
Serena Coschignano
Università degli Studi di Pavia. Dipartimento di Studi Umanistici,
Sezione di Linguistica Teorica e Applicata.
Corso Strada Nuova 65, 27100 Pavia.
E-mail: serena.coschignano@unibg.it

Multidisciplinary Research in Neurosciences

Against the Plausibility of Utilitarianism

Andrea Loffi
University of Trento, Neurotheoretic Group, Pavia (Italy)

Abstract. The aim of this paper is to discuss some highly intuitive thought experiments against the plausibility of utilitarianism in general and the role of suffering in moral reasoning in particular. Accordingly, it will be shown that deontology appears to be a more plausible normative theory. The meta-ethical problem of the role of intuitions in moral reasoning will also be considered.

Key words: Utilitarianism, deontology, moral intuitions, suffering, P. Singer, I. Kant.

Introduction

Utilitarianism is one of the most important aspects of current debate in moral philosophy and, more generally, in practical philosophy. It comes in a wide range of variants: act and rule utilitarianism, hedonistic and preference utilitarianism, average and total utilitarianism, etc. Nonetheless it is sufficient, for the purpose of this work, to refer to a minimal version that can be defined as follows: utilitarianism is a normative theory that prescribes as morally good those actions entailing, as their consequences, an increase in pleasure or well-being or happiness, and prohibits as morally bad those actions entailing, as their consequences, a decrease in pleasure or well-being or happiness (1, 2, 3).

The literature on utilitarianism is vast, as is the literature against it. Among the most compelling arguments against the so-called pig philosophy, we can cite the passage from F. Dostoevsky's *Brothers Karamazov*, according to which the innocent suffering of a single child cannot be justified even should it bring the whole world the greatest happiness; or the experience machine argument put forward by R. Nozick in *Anarchy, State, and Utopia*, namely that even if there existed an experience machine able to grant us the experiences we most desire (writing a bestseller, becoming an Olympic 100 meters champion, and so on), the simulated reality produced by it, being false, would ultimately be worse than actual reality (4). Here I intend to develop a much more modest, and much more intuitive, thought experiment against the plausibility of utilitarianism.

Stolen Cash

Let us imagine the situation of a wealthy man who goes to a cafe counter to pay for breakfast in the company of a friend, takes out his wallet and, distracted by the conversation, allows a five-euro bill to slip from his fingers and fall to the floor. Let us imagine that he does not notice – his wallet is always well stocked – and, indeed, that he will never notice that the banknote is missing. Let us then imagine that another person notices the banknote, and quickly picks it up off the floor.

The question is: how does utilitarianism evaluate this plausible situation? Since the wealthy man will not notice the loss of the banknote – the sum is negligible in relation to his overall wealth –, he will not suffer any negative consequences and his happiness will not diminish. Conversely, the man who took the

money will enjoy a slight increase in his happiness. It therefore follows that, for the utilitarian, this action, which essentially amounts to theft, is a good action.

From the perspective of common moral intuition, which is our immediate means of judging a situation or an action positively or negatively, this conclusion is surely repellent. How might the utilitarian respond to this? Before addressing this, let us first formalize my argument.

Premise 1: According to utilitarianism, the actions that maximize happiness are good.

Premise 2: Theft that goes unnoticed is an action that increases the happiness of the thief without decreasing that of the victim.

Premise 3: Unnoticed theft is a good action according to utilitarianism.

Premise 4: Theft in itself is intuitively a bad action regardless of the suffering it may cause.

Conclusion: Utilitarianism envisages at least some intuitively bad actions and is therefore an implausible normative theory.

Two Objections of the Utilitarian

Based on these premises, the utilitarian could raise two possible objections. I) He could reject the second and third premises, arguing that unnoticed theft in fact, at the end of the day, leads to a minimization and not a maximization of happiness: in fact, were unnoticed theft to be perpetrated systematically, in the long run it would end up being noticed, causing the same effects as outright theft. If the thief in our thought experiment scenario continued to steal small sums from our wealthy man, the latter would probably end up noticing it and thus his happiness would diminish. To this, however, one can easily reply that the utilitarian would still have no reason to judge unnoticed theft as bad in itself, and that if our thief were particularly prudent, stealing only a few sums or small objects, he would be, for utilitarianism, a good and happy man.

II) The utilitarian could also reject the fourth premise and the conclusion, arguing that our moral intuition is wrong and consequently claiming that unnoticed theft is in fact a good action.

Intuitions and Moral Intuitions

The utilitarian's last argument can be countered in various ways. It must certainly be conceded that intuitions, however widespread and generally accepted, can be erroneous. It is also true that philosophy is the rational mediation of thoughts, and therefore that intuition, being an immediate mental content, would appear to be incompatible with it. However, a distinction must be made: it is true that philosophy cannot consist of intuitions; a philosophy of intuitions would be a contradiction in terms. But it is wrong to think that philosophy should not, once it has developed its arguments, confront the intuitions that people normally have. After all, intuitions are an experimental ground for philosophy.

I say "experimental", but of course in this setting things are a little more complicated than in natural sciences. In laboratory experiments, facts have the last word. If a theory is not supported by facts, the theory must be revised or discarded. If my theory states that when I pronounce a certain formula, the light disappears, the air chills and objects begin to levitate, but facts disprove my theory, then I am forced either to revise or discard it.

Philosophy is another case altogether: there is a circular relationship between philosophical theories and the intuitions we commonly have. Our intuitions tend to be the starting point for philosophical investigation: a Christian, for example, starting from his religious faith, might try to elaborate a rational philosophy of religion that justifies that faith. If he succeeds, philosophy corroborates the intuition from which he started; if he does not succeed, he may decide to abandon his faith, or to try to develop a different philosophy of religion.

The same applies in the case of moral reasoning. Our intuitions immediately tell us what to do or not to do in a given situation, and it is on this basis that everyone acts in the overwhelming majority of situations in life: we do not push old people in the street because it seems wrong to us; we do not steal oranges from the market because it seems wrong to us. Kant himself argued that the task of the moral philosopher is not to discover what we should or should not do: we already know that, at least to some extent. The task of

the moral philosopher is not to subvert common moral intuitions, but rather to explain them (5).

Sometimes, though, some experience is at odds with our moral intuition, or we may be faced by two moral intuitions in mutual contradiction. Here, moral reasoning takes over, and tries, respectively, either to reconcile our intuition with our experience, or to clarify the contradiction between the two conflicting intuitions. To illustrate the first case, we might think, for example, of a Western tourist visiting a strictly Muslim country and feeling uncomfortable at the sight of veiled women. He might think that such treatment of women is unjust, because men and women should be treated equally. If he is unable to find any plausible objections to this view, then his intuition will be corroborated; if, on the other hand, he does come up with plausible objections, then his intuition will lose its immediate persuasive force; for example, our tourist might ultimately decide that different cultures have legitimately developed different forms of social relations and dress codes from those in the West.

The second case can be illustrated by the situation of someone who sees and is deeply disturbed by a documentary on intensive animal farming, and consequently feels caught in a dilemma between the permissibility of eating meat, something he might have always done and that seems absolutely normal to him, and a feeling of uneasiness over the cruel treatment of animals.

Returning to the thought experiment of the unnoticed theft, the question is whether we should give more weight to the obvious intuition that the action is bad, or whether we should instead accept the utilitarian's conclusion that the action is good when it is proven to be so, i.e., in certain circumstances. I would argue that the burden of proof falls squarely on the utilitarian, and frankly see no good reason why his normative theory should trump our absolutely reasonable intuition.

Deontology and the Moral Relevance of Suffering

My thought experiment should, then, be an argument against the plausibility of utilitarianism, but also indirectly an argument in favor of the plausibility of deontology: with some form of deontology, we can in fact very easily explain our intuition by asserting that unnoticed theft is wrong in itself, regardless of the suffering it may entail.

Here, however, we seem to be embarking on a dangerous slope. If, for deontology, suffering has no relevance in the moral evaluation of unnoticed theft, does that mean we can generalize and say that suffering has no moral relevance at all for deontology?

Let us consider the Kantian version of deontology. It prescribes that there are absolute duties, which can be summed up in the command always to treat humanity also as an end in itself, and never merely as a means. Deontology condemns our unnoticed theft because the thief is treating another man as a means to enrich himself. If, in accordance with Kant, we were to generalize, in the form of universal law, the maxim that led the thief to act, we would end up with a world in which theft is permissible as long as the victim does not notice it: not a particularly inviting world.

The utilitarian, at this point, may feel that the deontologist has contradicted himself: if the generalization of a maxim reveals its rightness or wrongness through the world that would hypothetically arise as a result, then deontology would seem to rest, ultimately, on evaluation of consequences. This idea is countered by a purely logical argument: a legal system in which unnoticed theft is lawful would be self-contradictory, because it would undermine the very peaceful civil coexistence that it is intended to guarantee and regulate. This logical self-contradiction also results in the pragmatic impossibility of wanting a world in which, according to our example, such theft can always occur (6).

The crux of deontology, at least in its Kantian version, is the notion that actions are right if and only if they are performed on the basis of duty alone. Even the fact of acting out of a feeling of benevolence makes the action itself, strictly speaking, immoral. This is highly intuitive: could a judge being sympathetic to, say, a murderer be considered just? Is it not more respectful of the murderer's dignity to treat him as a person fully responsible for his actions, without trying to relieve him of his responsibility because he had, say, a traumatic childhood or a bad divorce? On this basis Kant argued for the rightness of capital punishment (6).

If, then, suffering plays no role in the deontologist's moral assessments, what about animal rights, for example? In this regard, the utilitarian position boasts a high degree of plausibility: since animals suffer, they must be morally protected, and for example it can be argued that it is wrong to breed them for food. However, not all utilitarians are vegetarians, and some of them may object to vegetarianism, believing that if animals are bred following high standards, and if their killing is quick and painless, it would be permissible to eat them, because their total well-being outweighs the instantaneous suffering of their slaughter. If, on the other hand, we take a deontological stance, and if therefore animal suffering has no moral relevance, what good reason is there to treat animals well?

Common moral intuitions on this issue are ambiguous: for example, there is no universal agreement on the morality of killing of chickens for roasting or of drowning newborn kittens for the purpose of decreasing the feline population; although both are common practices, the latter is considered less morally acceptable.

Kant's argument against cruelty to animals rests on the fact that humans who show it are more likely to be cruel to humans as well (7). This is empirically debatable, but in principle acceptable, as it coincides with a concept taken from criminal psychology known as the "MacDonald triad": nocturnal enuresis, pyromania, and, indeed, zoosadism are suggested to be three alarm bells signaling a propensity to psychopathy in early childhood (8).

However, Kant's argument assigns no intrinsic moral value to animals, viewing them as mere means for human activity. Moreover, within Kant's deontology, animals cannot be granted rights because they are not moral agents, only moral patients, i.e., entities that can only undergo the actions of moral agents and, to a certain extent, respond to them. A dog, for example, will love (or hate) its human according to the way in which the latter relates to it; even a flower can maybe be considered a moral patient: does it not wilt if plucked?

The dichotomy between moral agents and moral patients perhaps offers us a clue as to how to resolve the problem. Deontology's fundamental rule can in fact be supplemented by something that it currently lacks. Its revised formulation would be: treat moral agents always also as ends and never only as means, and take care of moral patients. What exactly this care should consist of can be debated, but certainly such a reformulation of deontology's golden rule has at least two advantages. First, it guarantees a measure of protection not only to animals but to virtually every living being, without resorting to the concept of suffering. Utilitarian ethics cannot assign intrinsic value to inanimate nature, whereas deontology can, and this is absolutely in line with our intuitions.

The second advantage is that this version of deontology guarantees protection without placing a man and an oyster, or a woman and a Sidney funnel-web spider (*atrax robutus*) on the same level. Accusations of speciesism, i.e., of unfair discrimination that does not allow equal treatment of all animal species, or at least guarantees it only for the most neurologically developed ones, are frequent in current moral debate. Speciesism leaves me more than perplexed for at least one obvious reason: only humans, and maybe not even all humans, are moral agents, i.e., free, concerned with the meaning of their lives, and so on. This assertion seems evident enough to justify speciesism, at least in general terms, without of course legitimizing any form of cruelty to other living species.

All this suggests the rights that deontology ascribes to animals and to the rest of the living world should therefore be *sui generis* rights, whose specific difference from human rights should be defined.

A Further Word on Suffering

It may be objected that denying any moral relevance of suffering seems entirely contrary to our intuitions, and that, conversely, it is generally held to be self-evident that inflicting suffering is in itself evil. However, if one thinks about it carefully, the issue is not so clear-cut, and in this case, we find that it is precisely intuition that is a little off the mark. There are two concomitant arguments for the moral irrelevance of suffering.

The first, even trivial, argument is that in some cases suffering is useful or even good: e.g., when a child is forced to do his homework, when a rapist is punished, when a coach urges an athlete to do another series of push-ups. Suffering is neither good nor bad in

itself, as even utilitarians recognize when they say that a little suffering today (I refrain from smoking a packet of Marlboros a day) can maximize happiness tomorrow (I reduce my chances of getting lung cancer). There are even cases in which someone requires physical suffering to be inflicted, as in sadomasochistic sex, or inflicts it on himself to feel pleasure, as in masochistic autoeroticism.

The second argument has already been developed, and it is the cornerstone of this work: a bad action that does not cause suffering remains a bad action nonetheless. We have already been through the example of unnoticed theft, to which we could add countless others. Is a man who cheats on his wife without her finding out doing a good thing? Can a boy who plucks all the lilies in a flowerbed in an abandoned backyard be said to have performed a good action, since he enjoys doing it, the lilies do not suffer, and no passer-by can feel sorry that those beautiful lilies are no longer there?

Suffering in itself is not morally relevant; it is only the violation of the rights or dignity of a moral agent or patient that is relevant. A psychopath may tie a victim to a chair and torture her with hot irons, while another psychopath may tie her up and keep her in a continuous state of sedation so that she feels nothing. Is the second psychopath better than the first, or significantly better than the first, because he makes the victim suffer less?

Pleasure and happiness are not morally good in themselves: it is common knowledge, after all, that – as Kant put it – making a man happy is quite different from making him good. Nor, conversely, is suffering morally bad in itself. Again, in Kant's words: "It is impossible to think of anything at all in the world, or indeed even beyond it, that could be taken to be good without limitation, except a GOOD WILL" (5).

Two Concluding Arguments

To conclude, let us examine two more arguments against the plausibility of utilitarianism: the first could be called the "cognitive symmetry argument", while the second, once again, derives from a thought experiment.

Both arguments rest on a common premise. A normative theory, as Kant never tires of repeating, must be valid not only for human beings but also for all rational beings in general, and must prescribe universal norms. The utilitarian would not disagree in principle with this point: he, too, tends to recognize the universality of moral prescriptions against any relativism. In the language of metaethics this is called "cognitivism": cognitivism holds that moral judgments convey genuine knowledge, and therefore are as true or false as factual judgments (9).

Here, however, we run into the first problem: that of cognitive symmetry. A judgment such as "killing an innocent person is wrong" is always true for the deontologist, but not always true for the utilitarian. For the deontologist it is true in itself, whereas for the utilitarian it is true only under certain conditions, as in the case of "killing an innocent person is wrong unless, on the whole, the consequences minimize overall suffering". The utilitarian therefore has to explain why there is no cognitive symmetry between factual judgments, true or false in themselves, and moral judgments, true or false depending on the circumstances. For deontology, on the other hand, there is cognitive symmetry between the two spheres of judgments.

Of course, the utilitarian might object, for instance, that it is not true that all factual judgments have the same cognitive status. He might point out, for instance, that the laws of classical mechanics consist of judgments that are true provided they are applied to certain levels of reality, whereas they are no longer true at the level of quantum physics. This is certainly correct, but the fact remains that deontology offers greater cognitive symmetry between factual and moral judgments, and this symmetry seems more plausible than utilitarianism's cognitive asymmetry.

The second concluding argument derives from a thought experiment. Let us imagine a society of rational beings completely incapable of experiencing feelings of any kind: say, a society of technologically refined computers with personalities, or a society of bizarre incorporeal aliens, or a society of angels. The utilitarian would have to admit that such beings fall outside the sphere of morality simply because they are incapable of feeling. Therefore, destroying a computer endowed with personality would be per se a morally indifferent action.

Here again, utilitarianism does not seem to lead to

a very plausible conclusion. On the contrary, it could be said that utilitarianism is a speciesist normative theory, in that it only takes into consideration life forms capable of feeling pleasure and pain, while it discriminates against life forms (albeit hypothetical ones) that are rational, certainly, but not sensitive.

References

1. K. de Lazari-Radek, P. Singer, Utilitarianism: A Very Short Introduction, Oxford University Press, 2017.
2. P. Singer, Practical Ethics, Cambridge University Press, 1979.
3. L. Fonnesu, Storia dell'etica contemporanea. Da Kant alla filosofia analitica, Carocci, Rome, 2006.
4. R. Nozick, Anarchy, State, and Utopia. Basic Books, New York 1974.
5. I. Kant, Groundwork of the Metaphysics of Morals, edited by Jens Timmermann and Mary Gregor, Cambridge University Press, 2011, p. 15, 37.
6. V. Mathieu, Introduzione, in: I. Kant, Fondazione della metafisica dei costumi, edited by V. Mathieu, Rusconi, Milan, 1994.
7. I. Kant, The Metaphysics of Morals, translated by Marc Gregor, Cambridge University Press, 1991.
8. V. M. Mastronardi, R. De Luca, I serial killer, Newton, Rome 2009.
9. S. F. Magni, Bioetica, Carocci, Rome, 2011.

Correspondence:
Andrea Loffi, Ph.D. in Philosophy
University of Trento, Neurotheoretic Group, Pavia (Italy)
Viale martiri della libertà 22, 27035, Mede (PV)
E-mail: andrealoffi91@gmail.com

One century after Marian Lydia Shorey, a fleeting star at the inception of the long path to the discovery of Nerve Growth Factor

Marco Piccolino[1], *Isabel Murray*[2]

[1]Centre of Neurosciences of the University of Ferrara, Ferrara, Italy; [2]Department of Ecclesiology, Faculty of Theology, Stellenbosch University, Stellenbosch South Africa.

Abstract. This article, the third of a series dedicated to Rita Levi-Montalcini's and her discovery of the Nerve Growth Factor (NGF), deals with an almost unknown American scientist, Marian Lydia Shorey. In 1909, in her dissertation thesis at the University of Chicago, Shorey reported the results of experiments made on the chick embryo that set the stage for further research leading to the discovery in the 1950s of NGF. Thereafter, this discovery path was marked first by the work first of Viktor Hamburger, afterwards by Rita Levi-Montalcini and Giuseppe Levi, and eventually by the research of Levi-Montalcini and Stanley Cohen in Hamburger's lab in St. Louis. As we will see, despite the importance of Shorey's results, she disappeared from the annals of science largely stemming from the personal and social events of a sad life concluded tragically just one century ago, in 1922.

Key words: Marian Lydia Shorey, neuroembryology, Nerve-Growth-Factor, Rita Levi-Montalcini, Viktor Hamburger, Giuseppe Levi.

Un secolo dopo Marian Lydia Shorey, una stella fugace all'inizio del lungo cammino di scoperta del Nerve Growth Factor

Riassunto. Questo articolo, il terzo di una serie dedicata a Rita Levi-Montalcini e alla sua scoperta del Nerve Growth Factor (NGF), è dedicato alla storia di una scienziata americana quasi sconosciuta, Marian Lydia Shorey. Nel 1909, nella sua tesi di laurea all'Università di Chicago, Shorey riferì i risultati di esperimenti effettuati sull'embrione di pulcino che posero le basi per le successive ricerche che, negli anni '50, portarono alla scoperta dell'NGF. Dopo di lei, questo percorso di scoperta è stato segnato inizialmente dal lavoro di Viktor Hamburger, poi da quello di Rita Levi-Montalcini e Giuseppe Levi, e infine dalle ricerche di Levi-Montalcini e Stanley Cohen nel laboratorio di Hamburger a St. Louis. Come vedremo, nonostante l'importanza dei risultati di Shorey, la sua figura è scomparsa dagli annali della scienza in gran parte a causa delle vicende personali e sociali di una triste vita conclusasi tragicamente proprio un secolo fa, nel 1922.

Parole chiave: Marian Lydia Shorey, neuroembriologia, Nerve-Growth-Factor, Rita Levi-Montalcini, Viktor Hamburger, Giuseppe Levi.

In 1986, Rita Levi-Montalcini was awarded the Nobel Prize for the discovery of Nerve Growth Factor (NGF), a chemical agent released during the embryonic development, by certain peripheral structures capable of controlling the growth and differentiation of specific groups of nerve cells.[1] In her Nobel lecture, Rita made no mention of the fact that the experimen-

1 - On Rita Levi-Montalcini, besides the two articles already appeared in *Confinia Neurologica et Cephalalgica* (1, 2), see, moreover, a volume edited by Marco Piccolino in 2021 (3).

tal work leading her to that prestigious distinction was a continuation of the experiments carried out many years before by Marian Lydia Shorey, a young woman from Maine. (4) Shorey studied the development of the nervous system in the chicken embryo starting possibly in 1907 and wrote up the results in 1909 (the year of Rita's birth). (5) Her research was carried out at the University of Chicago, under the supervision of Frank Rattray Lillie, a prominent American zoologist, who was well known, particularly for introducing the chicken embryo as a model preparation in experimental embryology. Two years after her 1909 paper, Marian published another article, but thereafter she was forgotten by the scientific community, despite the fact that her experiments stimulated further significant research in the field of neuroembryology. (6)

In her Nobel speech, Rita gave appropriate mention to the role of two mentors in the discovery path of NGF. One was the famous histologist, Giuseppe Levi, her teacher at the University of Turin, who collaborated with her in crucial experiments carried out in a home laboratory, *a la Robinson Crusoe*, she established during the years of the last world war and of racial persecutions. The other was Viktor Hamburger, a prominent embryologist, who was Rita's mentor at the Washington University of St Louis, where she, together with Stanley Cohen, made the final experiments of NGF discovery. (1, 4, 7)

These three scientists, Hamburger, Levi and Levi-Montalcini were all of Jewish ancestry and worked under difficult conditions during the period of racial persecutions in Europe. In the path leading to NGF discovery, Hamburger and Levi represent a kind of intermediate link between Marian Lydia Shorey and Rita Levi-Montalcini.

In 1932, Hamburger took the occasion of a research fellowship from the Rockefeller Foundation to leave his native country then undergoing a massive nazification, and emigrated to America. The laboratory chosen by Hamburger for his research happened to be that of Lillie in Chicago, i.e. the same in which more than twenty years earlier Shorey made her experiments on the development of the nervous system in chick embryo.

In 1983, in a video interview at the Washington University of St Louis, Hamburger narrated to the interviewer, Dale Purves, the way it happened to him to enter the research path opened by Shorey's 1909 experiments and culminated many years later in the discovery of the NGF. After recalling that, in 1931, his mentor at the Freiburg University in Germany, the Nobel Prize winner Hans Spemann, had proposed him as a candidate for a Rockefeller fellowship to work in the Lillie's laboratory in America, Hamburger added:

That was extremely fortunate because Lillie's was the only laboratory in this country that worked with chick embryos, and in 1909, that means twenty-two years before I came here, he had a student who had tried to kill wing buds in the chick embryo to see how the nervous system was reacting. How Lillie ever got that idea, I don't know. Then, Miss Shorey, who did it, disappeared from the literature, so I couldn't ask her either.[2]

There are two main points of interest in this passage of Hamburger's interview. One is his curiosity about the way Lillie "ever got that idea" to launch the research which was carried out by Shorey as the subject of her PhD dissertation in the Chicago laboratory. The second point concerns how and why "Miss Shorey […] disappeared from the literature".

With regards to Hamburger's curiosity about the beginning of Shorey's experiments, a remark can be made. In fact, the theme and the plan of Shorey's dissertation experiments were a logical, and predicable, consequence of the embryological conceptions and of the experimental programs that Lillie had been developing in those years, as a research manager at both the Chicago Zoological Institute and at the Woods Hole Marine Biological Laboratory.

As already mentioned, Lillie, a pioneer in the field of developmental biology, had been instrumental in introducing the chicken embryo as a reference preparation. This he did especially with the publication, in 1908, of the volume, *The development of the chick, an introduction to biology*. Besides defining and systematizing the various phases of embryonic growth, in his book the American scholar promoted, against a consolidated tradition based mostly on morphological investigations, a

2 - The interview realized on June 30th 1983, can be found, in both oral form and transcript, at the following webpage: http://beckerexhibits.wustl.edu/oral/interviews/hamburger.html

dynamic and physiological vision of the study of development, which he defined as "developmental physiology" or "experimental embryology" (8).

Here is what he wrote in the introductory part of the volume:

Development is as truly a physiological process as secretion, and as such is to be studied by similar methods, mainly experimental. The limits of pure observation without experiment are soon reached in the analysis of such a complex subject as the physiology of development; experiment then becomes necessary to push the analysis of the subject farther, and to furnish the true interpretation of the observations. (ref. 8, pp. 7-8).

Summarizing his approach to embryological studies, Lillie considered, among the principles that underlie the growth of the embryo, the influence of extraorganic conditions on the formation of the embryo, and the effects of the intraorganic environment, i.e., of component parts of the embryo on other parts ("correlative differentiation").

This theme, already at the centre of Lillie's first studies on the chicken embryo, was based on a non-preformistic conception of embryonic growth. For Lillie – far from being programmed in every detail – the harmonic growth of organs or parts of organs depends on the reciprocal interactions of nearby structures and in their functional relationship, and this integrated, or "correlated" interaction is supposed to occur mainly by means of diffusion through the extracellular environment.

The chicken embryo, Marian Lydia Shorey and the birth of experimental neuro-embryology

The interdependence of the growth of parts of the organism was the theme developed by Shorey in her studies for the doctoral thesis, undertaken on the advice of Lillie, in the Department of Zoology in Chicago, and with the chicken embryo as the preparation of choice.

In line with the conception of "experimental embryology", Shorey conducted a series of experiments investigating the effects of the removal of peripheral structures on the development of the nervous system at the level of the spinal cord. Using fine sewing needles as electrocautery probes, the young scholar (Marian was 36 years old in 1909) destroyed the buds of one of the two wings in the embryo, leaving the other intact as a control. She found out that this manoeuvre led to a reduction in the number and size of the precursors of nerve cells (neuroblasts), in particular in the motor columns of the spinal cord and in the corresponding sensory ganglia (i.e. those normally assigned to the motor or sensory innervation of the wing). Based on a series of considerations, she interpreted these effects as due to a failure to grow (hypoplasia).

In search of an explanation for these effects (and focusing her attention mainly on motor cells), Shorey then selectively destroyed some segments of the muscle buds (somites), and noticed that – even when the destruction was complete – a substantial percentage of apparently intact cells (about 40 percent) remained in the corresponding spinal nerve segments. She attributed this effect to the action exerted on these nerve segments by the adjacent, undestroyed somites. Since there was no anatomical relationship of innervation between somites and mismatched nerve segments, Shorey concluded that the observed effects were a consequence of the action of a soluble factor that, through the lymph, diffused into the extracellular environment, reaching targets located at a distance from the injured structures.

In her words:

Differentiation of any cell must therefore occur because of a change in the chemical composition or physical properties of the lymph surrounding it. In the case of neuroblasts, the cells outside the medullary tube [that is, the spinal cord] are also differentiating and the products of their metabolism must change, either in kind or amount, and these products must enter the lymph. It is therefore evident that the presence or absence muscles in a given somite must influence the character of the medium surrounding the neuroblasts in its immediate vicinity, and thus a change in the chemical inter-actions may be effected. (ref. 5, p. 53).

Her conclusion was in line with Lillie's aforementioned conceptions, according to which the integrated growth of the parts of the organism depends on the composition of the so-called "intraorganic environment". With an *a posteriori* view, Shorey's explanation can be posited to depend on a specific chemical factor,

or factors, released from the growing muscle and acting as a messenger on the nerve structures responsible for its innervation. It must be noted, however, that the language used by the American scholar betrays the fact that she rather conceived of a possible nutritional-metabolic action of the factor released by the embryonic muscle tissue, rather than of a messenger-type chemical effect.

In her "integrative" and interactive conception of nerve growth (reflecting – as we know – Lillie's ideas), the American scholar went even further. Shorey denied the possibility that neuroblasts could emit the extensions destined to become nerve fibres, in the absence of the necessary metabolic substances released by growing muscles (or by other structures, for example the skin in the case of sensory nerve cells). She even dared to contest the results obtained two years before by Ross Granville Harrison with his pioneer studies of cell cultures. In his landmark experiments, Harrison had demonstrated that an isolated nerve cell is able to emit the fibre, independently on the action of other cells (Harrison, 1907). In Shorey's view, the normal growth of isolated nerve cells depended on the fact that the lymph used as culture medium contained factors capable of stimulating the growth of the cell and its processes.

Here's how she put it:

Harrisons experiments, described above, in which portions of the medullary tube placed in a drop of lymph developed nerve fibers, are open to the objection that the lymph necessarily contained products of the metabolism of various organs of the body, and it is therefore not certain, indeed it is improbable, that the neuroblasts were removed from the influence of end organs whose physiological activities were similar to those which they normally innervated. (ref. 5, p. 55)

To increase support to her interpretation, in 1911 Shorey published a preliminary report based – as she puts it – on a small selection "from a great numbers of experiments" conducted with in vitro culture methods. With these experiments, she believed to have proven that, in the absence of external chemical factors, nerve fibres do not develop properly. In her opinion, the experiments she carried out on urodele amphibians (*Necturus*) provided important support for her working hypothesis. She did not see any development of nerve fibres when the culture medium was not supplemented with an extract of ox meat. (6)

The highly critical position adopted by Shorey in relation to Harrison's conception of the "independent growth" of nerve cells (a conception that in the early decades of the twentieth century was amply supported by scholars), undoubtedly contributed to relegating her into a kind of limbo. Additionally, Shorey's data were in disagreement with studies on the effects of ablation of limb segments, obtained in the 1920s by the American scholar Samuel Randall Detwiler, a student of Harrison who had used for his studies another type of urodele amphibian, the *Ambystoma* salamander. (9-10)

In conclusion, without any doubt, Shorey's work contributed fundamentally to the path of discovery of the mysterious factor of neural growth discovered by Rita and her collaborators about fifty years later. Although conceptually still within the limits of the science of her time, the young American scientist had revealed an important (but slow to be fully recognized in subsequent studies) aspect of the factor controlling the embryonic growth of the nervous system, i.e. its chemical nature. As a matter of fact, in their initial studies on the ablation of peripheral structures in chick embryo, both Hamburger and Rita and Levi, had failed to recognize the chemical nature of the peripheral agent potentially capable of controlling the growth of the nervous system.

Hamburger, in his studies in Lillie's lab in Chicago in the 1930s, confirmed to a large extent Shorey's experiments, by using a more refined technique to extirpate the peripheral buds of the chick embryo. He proposed, however, a totally different interpretation of the action exerted by the peripheral structures on nervous development. (11) His hypothesis was based on the involvement of central nerve fibres of a particular type that would act as "pathfinders". These fibres would enter the peripheral tissues and would then somehow transmit to the nerve centres the stimulus responsible for neuroblasts growth. In the case of ablation of peripheral tissues, these pathfinder neuroblasts would fail to transmit the physiological stimulatory message and a reduced nerve growth would ensue.

This is the way Hamburger imagined the action of these fibres:

We must charge the end organs of these first pathfinders with the double task of locating the peripheral field, and, in some way, 'reporting' back centripetally to the central organ the approximate size of the field to be innervated. The fibers would communicate the result of their exploration to their own cell bodies which thus would become the first relay station for the stimulus to be transmitted. Under the influence of the stimuli these nerve cells, which are not yet fully differentiated, when they have sent out their axones, would undergo a morphological or physiological change. (ref. 11, p. 475).

As to Rita and Levi, in experiments carried out during the war period in the home laboratory, *a la Robinson Crusoe*, the two Italian scientists came to a conclusion different from Hamburger's, which – however – also excluded the intervention of a diffusible, chemical agent. They assumed that the degeneration of the embryonal nerve cells, that followed peripheral ablations, was the consequence of the impossibility of the growing nerve fibres to establish proper synaptic contacts with the peripheral structures (see ref. 3).

In Rita's subsequent studies, carried out after the end of the war, in Hamburger's laboratory in St Louis, the perspective eventually changed when the chemical nature of the trophic agent involved in these experiments became clear. This occurred following the utilization in these studies of mice carrying a particular type of tumour capable of inducing effects similar to those of the mysterious peripheral agent. The injection of tumour extract into the allantoidal cavity of the embryo was able to produce an extraordinary growth of cells and nerve fibres throughout the organism, in the absence of any direct contact between tumour cells and peripheral tissues. Moreover, a similar astonishing growth was produced in isolated nerve cells in culture when the tumour extract was added to the culture medium (the "halo effect"). Finally, the chemical nature of the nerve growth agent was confirmed by "immuno-sympathectomy" experiments, consisting in the suppression of the growth of the sympathetic system induced by the administration of antibodies against the chemical agent whose precise chemical structure was yet to be identified. (see refs 3 and 7)

These results revived, although in a modern and more specific form, Shorey's conception on the chemical nature of the agent involved in the ablation experiments in chick embryo.

Marian Lydia Shorey: fragments of the life of a woman scientist in the early twentieth century America

An unknown scholar

After the Nobel Prize awarded to Rita and Stanley Cohen for their experiments leading to the discovery of NGF, Shorey's name re-emerged in scientific literature from which she had disappeared many years before (as remarked by Hamburger in his 1983 interview). However, until very recently, almost nothing was known of the life and career of Marian Lydia Shorey, and the few biographic elements sporadically found in articles and websites are often sources of error.

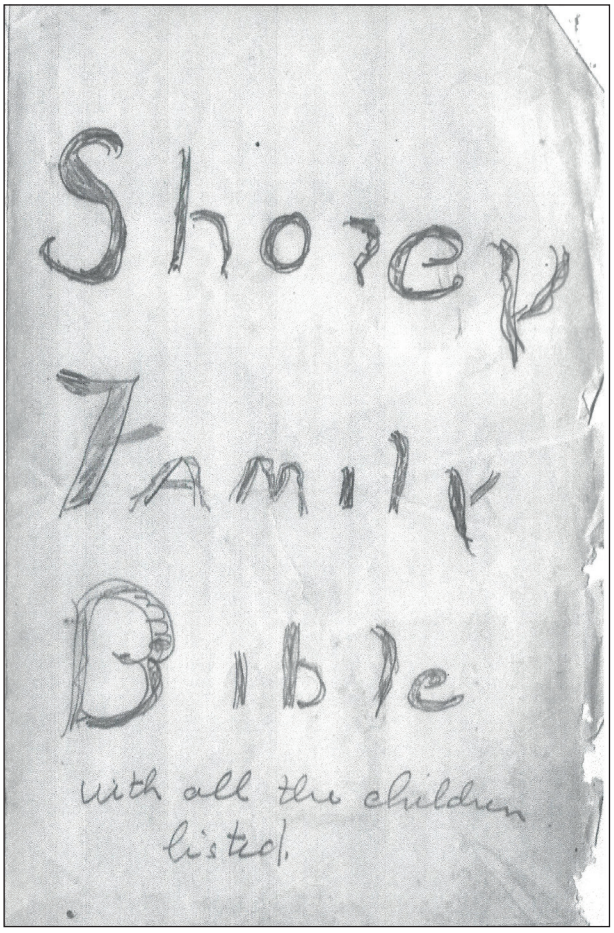


Figure 1. The title page of the manuscript "Shorey Family Bible", containing information on the Shorey family since the end of the eighteenth century.

The name is frequently misspelt (Marion, Mariam), or frankly wrongly written (Elizabeth)[3]. Sometimes, she is even assumed to be a male researcher by people who quote "his" work, probably without reading "her" papers.[4]

Things have changed in a substantial way with the research on Shorey's life that one of us (M.P.) started three years ago in collaboration with Germana Pareti of the University of Turin. This article, written one century after Shorey's death, is an attempt to draw her figure out from the darkness of the times and, in some way, to beget her a posthumous historical justice.[5]

Our research on Shorey has involved a search of all possible places and institutions that might provide information on her life and career, encompassing the consultation of books, journals, local reports, directories of scientific societies, "College Yearbooks", newspapers, census registers, lists of passengers of transoceanic ships and genealogical sites. In the end, it was not unfruitful, thanks to the competence and kindness of many persons around the world, from North America to South Africa. Among them Lisa Simpson Lutts, Debra Morehouse, Carolyn M. Picciano, Erin K. Dix, Cornelis Plug, Raymond Butti, Joseph Doore and many others who have actively collaborated in the attempt to add fragments to an incompletely documented biographical portrait.

Marian's life has emerged as a kind of painful counterpoint to the "luminous" story of Rita, who – as already mentioned – was born precisely in 1909, the year of publication of Shorey's thesis work.

Settlers in the Northeastern regions of the U.S.A.

Unlike Rita Levi-Montalcini, Marian Lydia Shorey was of a modest social background. She belonged to a large family of farmers and lumberjacks of Albion, Maine), in the Northeastern United States), and had managed to embark on a research career through a complex and difficult educational background.

Marian's ancestors had settled in Albion in the early 19th century. The first Shoreys to arrive in this region, very rich of forests and water, were Daniel, Edmund and Phineas Shorey (21, 19 and 17 respectively), three out of the ten children of Samuel Shorey

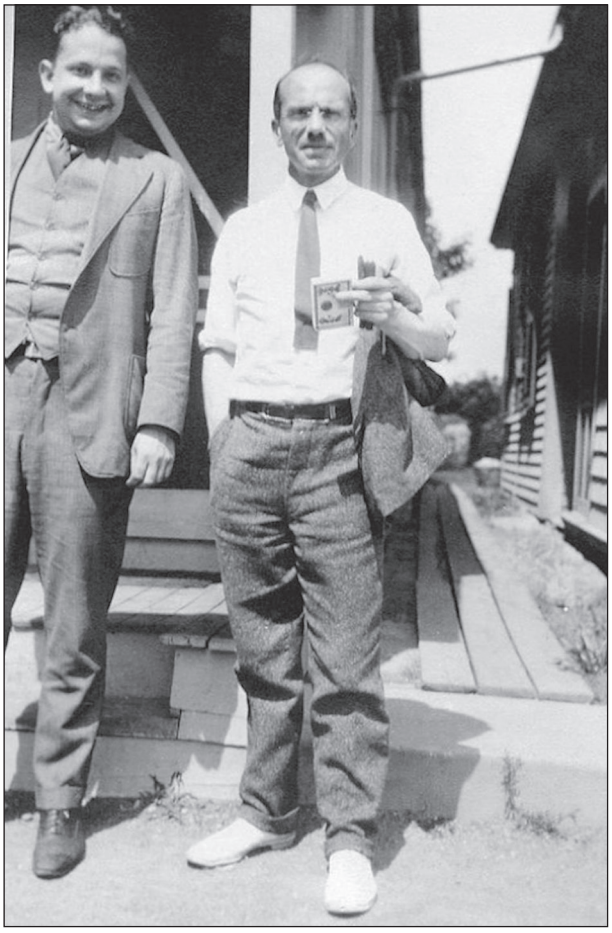


Figure 2. Frank Rattray Lillie, 1870-1947, (on the right) together with a colleague in a picture from the Archives of the American Philosophical Society ©.

3 - See for instance Lijing Jiang in the "*Embryo Project Encyclopedia*" web-site: https://embryo.asu.edu/pages/viktor-hamburgers-study-central-peripheral-relations-development-nervous-system

4 - In the 1909 paper (ref. 5), the one alluded to by Hamburger in his interview (and the first of the two articles authored by her), the names of Marian Lydia Shorey are indicated in full. However, in the index of the volume VII of *Journal of Experimental Zöology*, she is indicated as M. Louise Shorey. In the second paper the second name (Lydia) is indicated only by the initial. The error of alluding to Shorey as a male author occurs for instance in a book on the scientific and social aspects of biology published in 2001 by Garland E. Allen and Jeffrey Baker (ref. 12). The error is repeated by Allen, a student of Viktor Hamburger, in a historical paper on his teacher's life and work published in 2004, (ref. 13).

5 - Trying to put in the light of history a personage almost entirely "disappeared" (except for two scientific articles she left) has been as making a work somewhat similar to that done by Patrick Modiano for another lost female personage, Dora Bruder. Dora was a Jewish teen-ager disappeared in the 1941 Paris under the Nazi occupation, and eventually reappeared, just to be deported to Auschwitz in 1942 and vanish in the tragedy of the Shoah. (14)

and Elizabeth (Betsey) Woodsum.[6] They had left their home and their parents in Berwick Maine, about 130 miles south, and were proceeding north, looking possibly for a land grant on which to build a farm and thus settle (Crosby Wiggin, 1963). (15)

After having being informed that there was a property of about 600 acres in the southwest of Albion that could be obtained without money, Daniel and Phineas decided to settle there. They engaged to fulfil the legal and residential requirements needed to obtain it (which included, among others, "[to] build a sawmill and erect a house"). Edmund decided to go farther north, while Daniel and Phineas eventually built the required house and the mill near a waterway and forest. Daniel married Betsey Howe in 1810, and the two they had many children (13) as often was the case for settlers in strong need of prospective labourers for their farm.

The ninth child was Gustavus Benson Shorey, Marian's father, born in 1827. Gustavus married Julia Howe in 1852, from whom he had six children. At some point, Gustavus was obliged to build a second mill, after the first one was destroyed by a flood. Julia died in 1864, and, in the next year, Gustavus married Mary Ellen Gilman (20 years old at the time of the wedding). Marian Lydia was the third of at least nine children of Gustavus and Mary Ellen. In the 1880 census of Albion, eight children were listed as living with their parents (four daughters and four sons, these last ones all termed "labourers").

Marian was born in Albion on 6 February 1873. This date is certified by two passport applications signed by Marian herself. In various genealogical repertoires, accessible online, the year is incorrectly indicated as 1872, although the day and month generally are correct. In the register of Brown University, the institution where Marian graduated and taught at the beginning of the twentieth century, the year is indicated as 1873 in the "Graduate Records" (i.e. the correct one), but as 1874, in other documents (which also have a wrong date of birth, 4th instead than 6th February)

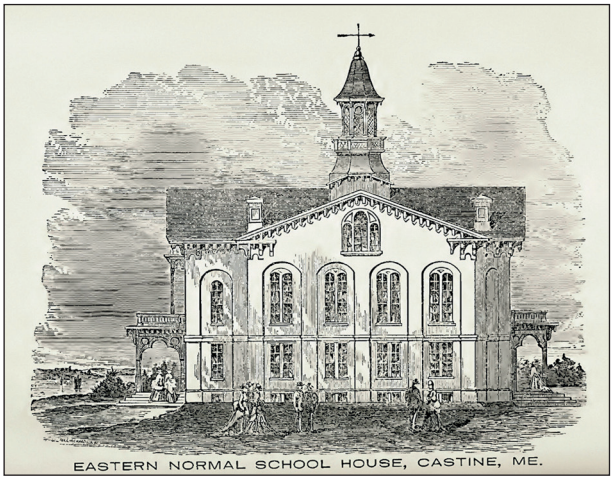


Figure 3. An old print featuring the State Normal School building in Castine, Maine, where Marian Shorey studied to get her teaching degree and to prepare for her admission to Brown University. The school has been active from 1867 to 1942.

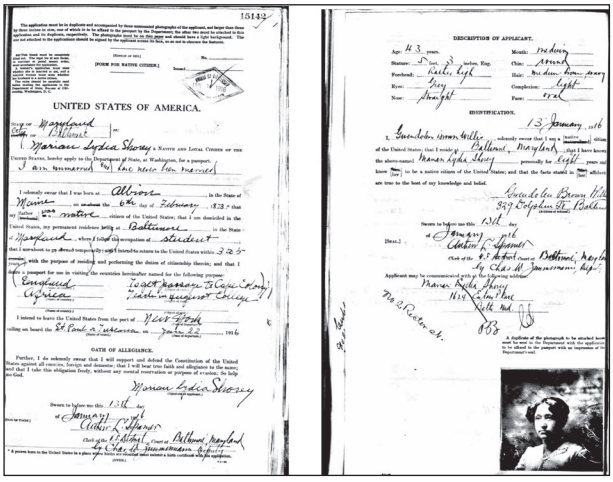


Figure 4. One of the two available passport applications in which Marian Lydia Shorey "solemnly swear[s]" to have been "born at Albion, in the State of Maine, on 6th day of February 1873. The application was made on 16th January 1916 and concerns Shorey's plan to emigrate to South Africa in order to teach at the Huguenot College of Wellington (see below).

Marian and her sister: studying and teaching, and studying again

Nothing is known of Marian's initial education, but we can assume that in her youth she attended one of the local rural schools. From the outset, she was probably interested in culture and perhaps science, and was proficient in her studies, which accounts for the fact that her life did not take the ordinary direction of

6 - If Daniel (Shapleigh) Shorey was really 21 years old, this foundational event should have occurred around 1819, because we know that he was born on 20th August 1788,

marrying at an early age, and producing and educating a flock of children.

In 1889, at less than seventeen years, and soon after finishing High schools, Marian began her profession as a teacher, almost certainly as a substitute teacher, in a primary school "of District n. 10" of her native village. The experience lasted a few months, but it must have been satisfactory. In the *Annual Report of the Municipal Officers and Supervisor of Schools, of the Town of Albion, for the Year Ending March 7th, 1890*, the inspector in charge of the control of that district, a certain T. Sanborn, evaluates the activity of the very young teacher this way:

Summer term, Miss Marion L Shorey, teacher. This was her first term. Though young in years, she came to her school possessing natural and acquired qualifications for her work, and I believe the school accomplished as much as though it had been placed in experienced hands. Miss Shorey will rank with our best teachers. (ref. 16, p. 12)

In 1890, at the end of this first work experience, Marian enrolled in the "Eastern State Normal School" of Castine, a small town on the Atlantic coast, in the Penobscot Bay, about a hundred kilometres from Albion. The "Normal schools" had been established, on the French model, to train teachers to be assigned to middle-grade educational institutions. Marian's choice is likely due to the fact that – as for other young women of her time in America (including her elder sister, Bina May) – the girl envisioned that, as a teacher, she could engage in an intellectual profession widely open to women. It offered her the opportunity to escape the status of wife and mother to which she, by birth, was destined as a peasant or worker.

It should be noted *en passant* that, although literary teaching prevailed in Normal schools, in the particular case of Castine there was a significant curricular addition dedicated to scientific culture. This was due particularly to the presence of a cultured teacher, Edward Everett Philbrook. A physician, graduated at the Boston School of Medicine, Philbrook was an eminent personage of the local community of Castine (as well as exponent of the Mason Grand Lodge of the Maine). He also had administrative duties in the Castine School, and he acted as a chairperson of the local committee of the Maine State Board of Health. He was a brilliant teacher, and – as reported, in 1934, in his Obituary in the *Bangor Daily News* – he was "beloved by hundreds of students all over the New England". In addition to scientific disciplines, he also taught music, being an expert musician and acting as director of choir in the local Congregational Church.

Figure 5. Marian Lydia Shorey (left) and her older sister Bina May Shorey (right) in their official portraits of graduation at the Castine Normal School. Marian and Bina were 21 and 26, respectively, at the time of these photos. As indicated below the portraits, the photos were taken in Belfast, a small town in Maine, about 40 km from Albion, in the studio of W [illiam] C [ain] Tuttle. At that time the studio was run by Adrian Cain, William's son who died in 1901.

Figure 6. Edward Everett Philbrook, a natural science teacher at the Eastern State Normal School in Castine at the time of Marian.

The table in Fig. 7 enumerates the courses of the Castine School which ranged over a great variety of disciplines both in the humanistic and scientific fields, with a rather evident predominance of the latter. Out of 33 courses, 17 had a clear scientific character, and only 12 could be assigned to the field of human sciences, with two courses in the arts (Music and Drawing). As was usual in normal schools of the time, there were also courses of a practical nature ("School Economy", Bookkeeping, Didactics of Education). In the last year of school, before graduating, the students had to carry out a period of "practical teaching" in the "model class" attached to the institute, an experience which, according to the school regulations, constituted a "good preparation for the work there" (*ibid.*, p. 16). From the *Catalogue and Circular of the State Normal School at Castine, Maine, for the Year Ending June 7, 1894*, it is clear that a model school was created *inside* the buildings of the Eastern State Normal School of Castine. Its purpose was such that "during their last year in the school, the pupil teachers find here an opportunity to do the actual work of the schoolroom, under kind and careful criticism" (ref. 17, p. 45).

Having graduated from Castine in 1894, Marian began her career as a teacher, which most likely took her to various places in the Northeast, including the town of Southborough in Massachusetts. Her name appears in the 1896 Census, with the qualification of "teacher". In the same year, Marian was listed among the residents of Southborough Mass. as a teacher, "boarding in the house of Fontinelle Carpenter". In addition, her sister, Bina May had moved southwards, since in the 1900 Census she was listed as living in Northampton Mass. the county seat of Hampshire County, as "teacher" boarding in the house of Charles Howard.

After a few years, however, Marian left teaching and decided to continue her studies at the university level (Bina May took the same decision). In 1900, Marian was admitted to Pembroke College, the women's division of the prestigious Brown University in Providence, where she attended natural science courses. During her university studies (which led her to obtain a Bachelor's degree in 1904, and – in 1906 – a Master degree "in Physiology, Bacteriology and Organic Chemistry"), Marian was active in the student organizations of the College, and, during the period 1904-1906, participated in teaching activity as an "instructor in physiology and household economics".

The subject taught by Marian, which was then also denominated by the more qualifying term "Euthenics", corresponded to a type of discipline placed at the intersection of various sciences: biology, medicine, chemistry, public hygiene, economics and even architecture. It was flourishing at the time, as part of a movement to promote the role and self-awareness of women in American society. As a matter of fact, it represented a compromise that allowed women access to scientific studies, within the limits of classic female roles, revolving around the house and the family, albeit in an apparently more modern form.

Marian's commitment to this type of teaching explains her participation, in June 1906, in the *Seventh Annual Conference of Home Economics* in Lake Placid, a tourist village in the State of New York. In her speech at this conference, Marian focused in particular on the issues of nutrition, public and personal hygiene, disciplines to be considered by the women attending the Conference as "guiding principles [that], as intelligent women, they may apply in conducting a home" (p. 81).

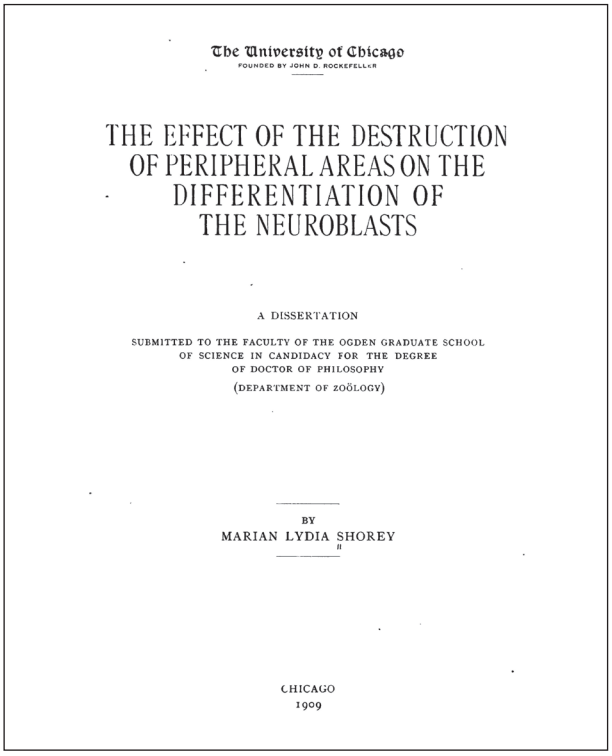
F Class	E Class	D Class	C Class	B Class	A Class
Arithmetic	Arithmetic, methods	Algebra	Geometry	Psychology	Didactics of Education
Grammar	Grammar	Geometry	General History	Chemistry	History of Education
Geography	Geography	Physics	Physics	U.S. History	Practice Teaching
School Economy	Algebra	Physical Geography	Rhetoric	Civil Government	English Literature
Reading	Physiology	Drawing	Botany	Moral Philosophy	Astronomy
Writing			Bookkeeping	Practice Teaching	Geology
Elementary Music					

Figure 7. A table with the courses assigned to the different classes of the Eastern State Normal School of Castine, in the years in which Marian Lydia Shorey attended the school.

These themes give us the measure of the limits to which this young woman (she was 33 years old at the time), educated and intelligent and interested in science, felt constrained in the minor role of Euthenics instructor. They permit us to understand the circumstances that underpinned the decision to change the direction of her life, by opting to continue her university studies. In 1906, she enrolled in a doctoral program at the University of Chicago, one of the most prestigious centres of biological research in the United States, where she obtained the PhD in 1909, under Lillie's tutelage.

The PhD in Chicago and the dream of a scientific career

The attainment of a doctorate in a prestigious institution, with the academic honour of publication of one's thesis, and the high-level research activity that she conducted in both Chicago and Woods Hole under the Lillie's aegis, certainly constituted a success for this farmer's daughter. Almost certainly this gave Marian a glimpse of the possibility of a scientific career in the academic field, an event that was then extremely rare for a woman, and – in particular – for a person emerging from disadvantageous socio-economic con-



The University of Chicago
FOUNDED BY JOHN D. ROCKEFELLER

THE EFFECT OF THE DESTRUCTION OF PERIPHERAL AREAS ON THE DIFFERENTIATION OF THE NEUROBLASTS

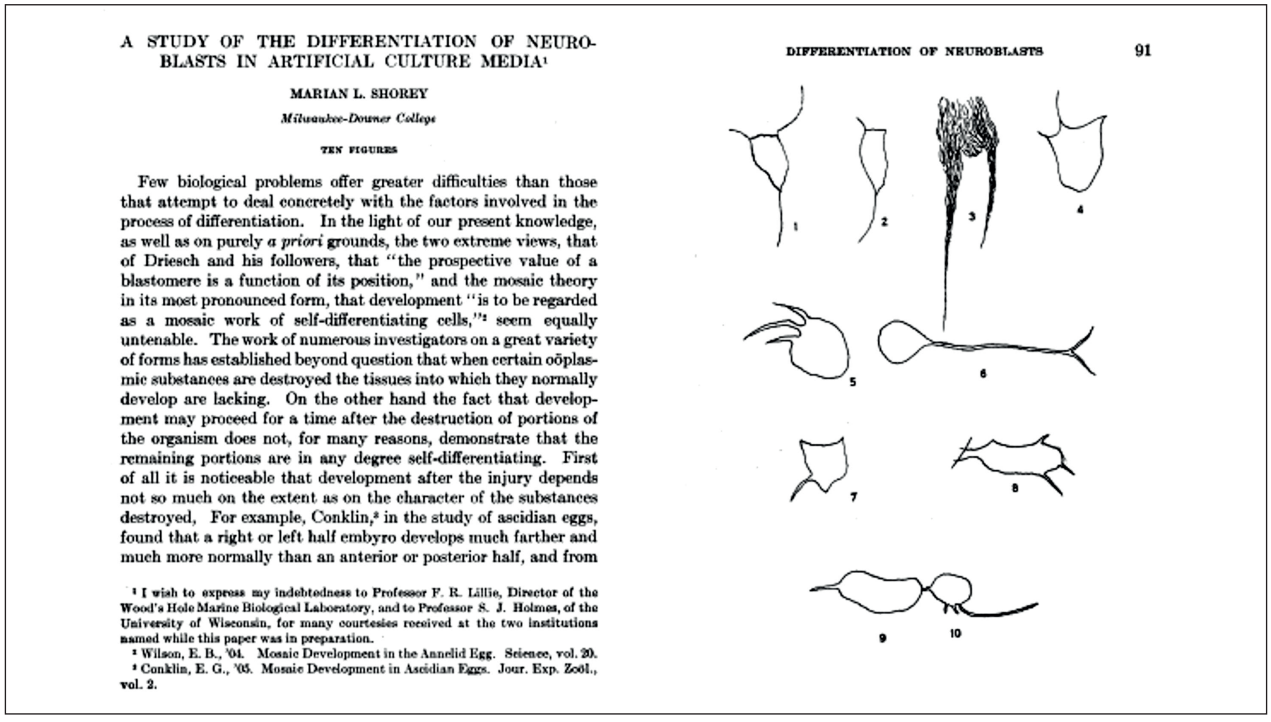
A DISSERTATION

SUBMITTED TO THE FACULTY OF THE OGDEN GRADUATE SCHOOL OF SCIENCE IN CANDIDACY FOR THE DEGREE OF DOCTOR OF PHILOSOPHY
(DEPARTMENT OF ZOÖLOGY)

BY
MARIAN LYDIA SHOREY

CHICAGO
1909

Figure 8. The title page of the doctoral thesis discussed in 1909 by Marian Lydia Shorey at the University of Chicago.



A STUDY OF THE DIFFERENTIATION OF NEUROBLASTS IN ARTIFICIAL CULTURE MEDIA[1]

MARIAN L. SHOREY

Milwaukee-Downer College

TEN FIGURES

Few biological problems offer greater difficulties than those that attempt to deal concretely with the factors involved in the process of differentiation. In the light of our present knowledge, as well as on purely *a priori* grounds, the two extreme views, that of Driesch and his followers, that "the prospective value of a blastomere is a function of its position," and the mosaic theory in its most pronounced form, that development "is to be regarded as a mosaic work of self-differentiating cells,"[2] seem equally untenable. The work of numerous investigators on a great variety of forms has established beyond question that when certain oöplasmic substances are destroyed the tissues into which they normally develop are lacking. On the other hand the fact that development may proceed for a time after the destruction of portions of the organism does not, for many reasons, demonstrate that the remaining portions are in any degree self-differentiating. First of all it is noticeable that development after the injury depends not so much on the extent as on the character of the substances destroyed, For example, Conklin,[3] in the study of ascidian eggs, found that a right or left half embyro develops much farther and much more normally than an anterior or posterior half, and from

[1] I wish to express my indebtedness to Professor F. R. Lillie, Director of the Wood's Hole Marine Biological Laboratory, and to Professor S. J. Holmes, of the University of Wisconsin, for many courtesies received at the two institutions named while this paper was in preparation.
[2] Wilson, E. B., '04. Mosaic Development in the Annelid Egg. Science, vol. 20.
[3] Conklin, E. G., '05. Mosaic Development in Ascidian Eggs. Jour. Exp. Zool., vol. 2.

DIFFERENTIATION OF NEUROBLASTS 91

1 2 3 4 5 6 7 8 9 10

Figure 9. On the left, the initial page, and on the right, a table with the figures from the article published by Marian in 1911, on the in vitro cultivation in different culture media of spinal cord explants obtained from the urodele amphibian *Necturus*.

ditions. Unfortunately, this possibility failed to materialize. In fact, the second article that Marian published in 1911 (6) represented her last scientific work, and afterwards, to use Hamburger's words, "Miss Shorey […] disappeared from literature").

Marian left Lillie's laboratory rather soon, perhaps due to financial difficulties or a lack of career prospects. Her research activity apparently continued for a while with research stages in Wood Hole (where – according to the records of the Marine Biological Center – she occupied a post in 1910), but, as early as 1908, she began a teaching career as a professor of biology and zoology in Milwaukee-Downer College, Milwaukee, Wisconsin. This institution had boasted a long tradition education that focused on the objectives that constituted the preferential tasks in the professions or roles intended for women: teaching, nursing, childcare and housekeeping. It was certainly not a place in which to continue high-level experimental research, such as the program Marian had been able to undertake during the Chicago years.

Figure 10. Portrait of Mary Lyon (1797-1849), the energetic and intelligent founder of the Mount Holyoke Seminar for the education of young women.

What happened next is somewhat mysterious, and marks the beginning of a descending parable bound to have a sad conclusion one hundred years ago, in 1922. In 1915, a short note in the *College Bulletin* (Milwaukee-Downer College) informs us of the fact that Shorey resigned her teaching post: "Marion (sic) Shorey (prof. of Zoology) has resigned" (this is despite the fact that her name still appears as secretary of the Club of Milwaukee until July 1916). In this same year, a brief note in the same *Bulletin* says: "Dr. Shorey, formerly connected with the Faculty of Milwaukee-Downer College, is in Baltimore studying and resting". The allusion to the "resting" condition could suggest that Marian was suffering from some disease, and thus needed to leave her research activity for a period.

Very likely, however, this was not the case.

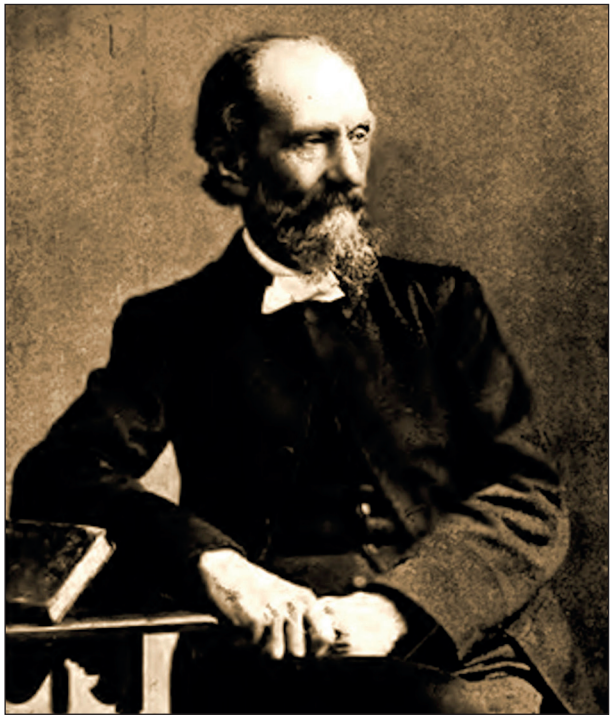


Figure 11. Andrew Murray (1828-1917), the "Moderator" of the Dutch Reformed Church of South Africa, who played a pivotal role in the creation of Huguenot Seminary, South Africa's first higher education institution for women, which later became Huguenot University College (is the revelant name in Shorey's time).
Since the name changed numerous times and thelongside/apart from the 'college' long after the College was added, I think it more accurate to - for this article and time frame - stick to the actual name of the institution where Shorey taught..

Emigration to the southern regions of the world

The reasons for this unexpected move by Marian can be understood on the basis of the decisions that matured during her stay in Baltimore. This period evidently represented for her a necessary pause for reflection at the moment of an important choice in her life, that of leaving America for a few years in order to go and teach in another and distant continent. On January 13, 1916, Marian applied to obtain a passport, specifying in the application that she intended to travel to South Africa to teach at the "Huguenot University College" in the Cape Colony. The fact that she declared Baltimore as her permanent residence at the time of the application, and as her occupation that of a "student", suggests that during her stay in this city Marian attended university courses to prepare herself adequately for the teaching that she would subsequently have to carry out in the South African college.

Although surprising, Marian's choice is quite understandable if one takes into account, on a general level, the great mobility that already characterized the world of Anglo-American university teaching at the time. More specifically, we need to consider the strong links that existed between the college where she went to teach (Huguenot University College or Hugenote Universiteitskollege in Afrikaans – in Wellington in the Cape region) and an important American institution for high-grade women education, Mount Holyoke College of South Hadley, Massachusetts, to which Marian was probably connected.[7] Mount Holyoke was an institution of female education, which – both in intention and in facts – went well beyond the limits of the classic training programs needed to prepare "good women and good mothers".

The Mount Holyoke institution was founded in 1837 by Mary Lyon, a young woman (like Marian, from a family of farmers) with a strong interest in teaching and promoting women's rights, and with an intense religious motivation in the context of progressive Protestantism. A characteristic of the Mount Holyoke education was a great emphasis on scientific teaching and experimental demonstrations, and, moreover, the importance given to manual work and physical exercise in the open air. (19-20) According to some of her biographers, one of Mary's favourite mottos was "First the kingdom of God, but after that—and after that most certainly—all science and knowledge"[8].

Around 1870, when the need to create university-level female teaching institutions began to be felt in South Africa too, Mount Holyoke was chosen as a reference model by Andrew Murray, the "Moderator" of the Dutch Reformed Church. (21) The first school he founded, the Huguenot Seminary, began its activity with the arrival in Wellington in 1873 of two teachers sent by Mount Holyoke, Abbie Park Ferguson and Anna Elvira Bliss. Abbie and Anna were the first of about 30 young American women to join the teaching staff of Huguenot Seminary and College in the following years. (21-24) Among these, in 1916, there was also our Marian. It is no coincidence that there were recruiters in America specially appointed by the leaders of the Dutch Reformed Church to identify potential teaching staff for Huguenot College. Almost certainly, the person who contacted Marian was one of these recruiters, Sarah Landfear. It is possible that one of the reasons convincing Marian to leave the Milwaukee-Downer College and go to South Africa was the concrete possibility to establish a research laboratory at Huguenot College. Indeed, there was a great deal of excitement in those years to equip a modern Department of Zoology in the College of Wellington, which was also to include experimental laboratories.

Although there is no indication of possible philanthropic reasons behind Marian's decision to go to South Africa, it must be taken into account that – starting from the beginning of the twentieth century – an element that pushed young women with humanitarian impulses to reach the African country was the situation of extreme life conditions of Boer women. Following the Anglo-Boer wars, many of them were interned in concentration camps, after the destruction

7 - This possibility is supported by the fact that, in a newspaper article on the death of Marian's sister, Bina May, appeared on *The Greenfield Recorder* of 22 November 1916 (see later), it is said that Bina May "Shorey was a graduate of Mount Holyoke College". As a matter of fact, Bina May and Marian had parallel paths in their education.

8 - The strong interrelations between progressive forms of religion or spiritual philosophy and the social and women rights movements (typical of many initiatives of the nineteenth-century America) are attested, among others, by the success of the novels of Louisa May Alcott, that were widely read in her native country (and elsewhere). Alcott's writings and personal life contributed to lay the cultural grounds, for the young women of the epoch, of a new conscience of their rights and capacities.

of their villages and the massacre of Boer men by the British. Among the prominent personalities who at the time brought South Africa and Boer women to the centre of international attention was in particular Emily Hobhouse, a humanitarian activist from an English aristocratic family, who visited the country and the numerous concentration camps set up by the British government in various territories of South Africa. Nicknamed "the Gandhi of South Africa" for her tireless activity, Emily strove in various ways to improve the conditions of Boer women. In addition to raising money for them, she organized schools to teach young women the art of weaving and spinning, also attracting attention and help to these initiatives from other countries, and in particular from Italy. (see ref. 21)

Similarly, although no clear indication could be found of Marian commitment to religion, it is likely that, at least to a degree, her decision to leave for Africa was in some way influenced by the popular trend amongst religious young North American professionals to "go to Africa to reach and educate the heathen".

Whatever the case, Marian left America on January 22 by ship from New York to Liverpool, where she arrived eight days later, waiting to embark on her new destination, distant South Africa. However, it is possible that she took advantage of the stop in England to go to London, as a letter from Sarah Landfear in April of that year seems to indicate.

Figure 12. The "American Line" Ocean Liner Saint Paul, the ship with which Maria Shorey sailed from New York on January 22, 1916, and reached Liverpool on January 30. Launched in 1895, it was an elegant and comfortable passenger ship used for transoceanic passages. In October 1917, the Saint Paul was transformed and employed for World War I warfare operations by the US Navy.

We know from Landfear's correspondence that, when deciding the trip, she also took into account the possible dangers represented by the state of war in which the whole world – and Europe in particular – was at that time. These dangers in fact loomed if one recalls the raids by German submarines (the fearsome *Unterseeboot* or U-boots) which came up to the coastal waters of Brazil and also to the fact that the ship that

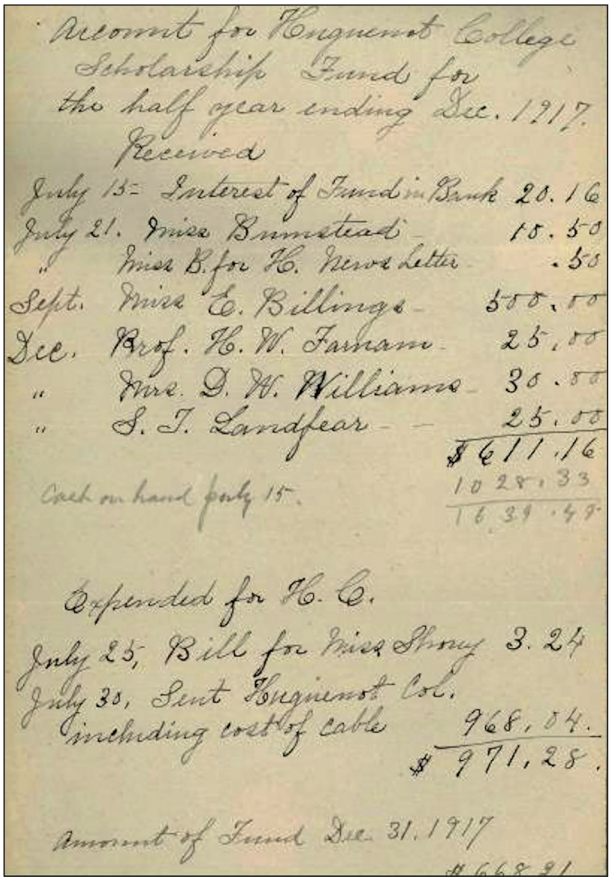
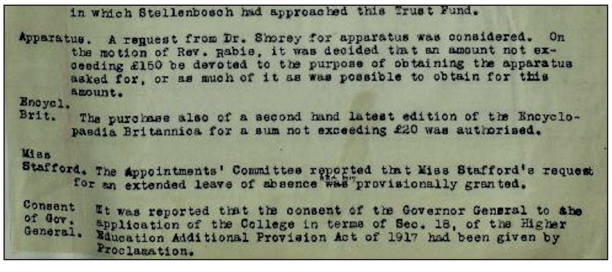

Account for Huguenot College
Scholarship Fund for
the half year ending Dec. 1917.
Received
July 15 Interest of Fund in Bank 20.16
July 21. Miss Bunnstead 15.50
" Miss B. for H. News Letter .50
Sept. Miss E. Billings 500.00
Dec. Prof. H. W. Farnam 25.00
" Mrs. D. W. Williams 30.00
" S. T. Landfear 25.00
$611.16
Cash on hand July 15. 1028.33
1639.49
Expended for H. C.
July 25, Bill for Miss Shorey 3.24
July 30, Sent Huguenot Col.
including cost of cable 968.04.
$ 971.28.
Amount of Fund Dec. 31. 1917
$668.21

Figure 13. The note of the payments made to Marian for her outward trip to South Africa.


in which Stellenbosch had approached this Trust Fund.

Apparatus. A request from Dr. Shorey for apparatus was considered. On the motion of Rev. Rabie, it was decided that an amount not exceeding £150 be devoted to the purpose of obtaining the apparatus asked for, or as much of it as was possible to obtain for this amount.

Encycl. Brit. The purchase also of a second hand latest edition of the Encyclopaedia Britannica for a sum not exceeding £20 was authorised.

Miss Stafford. The Appointments' Committee reported that Miss Stafford's request for an extended leave of absence was provisionally granted.

Consent of Gov. General. It was reported that the consent of the Governor General to the application of the College in terms of Sec. 18, of the Higher Education Additional Provision Act of 1917 had been given by Proclamation.

Figure 14. A detail of the November Huguenot Council minutes with a request made by Marian in order to obtain materials for the Zoology laboratory.

transported Marian to England in 1916 was converted the following year into a warship.

We do not know the details of the second passage to the African continent, and we do not even know the exact date of Marian' arrival in Cape Town. However, from correspondence between Miss Landfear and Miss Allen (Huguenot College) dated January and April 1916, it can be inferred that it was only toward the end of April 1916 – even though Marian was officially appointed in January to commence her post of teacher (Lecturer) at the Huguenot College in March 1916.

In the "Staff record" of Huguenot College, Marian's details are given as follows:

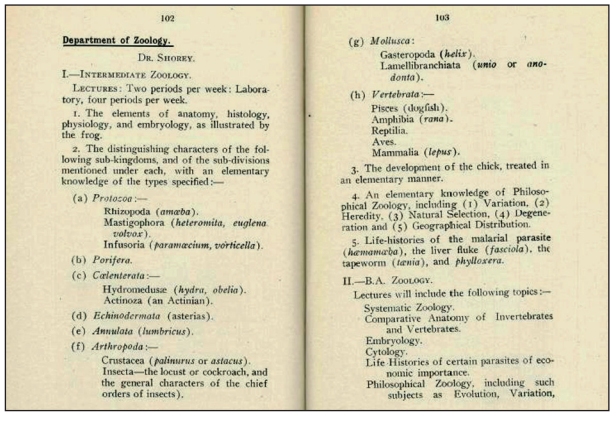
Shorey, M.L. PhD (Chicago)
Lecturer in Zoology
Appointed January 1916
(Resigned January 1918)

The first certain mention of Marian's teaching involvement in Wellington is from the Huguenot College Council Meeting report, dated May 1916, and concerns a request she made to obtain funding from the Department of Zoology.

Almost certainly, apart from teaching, the effort to establish a research laboratory at Huguenot College was one of the major commitments that absorbed Marian during her time in Wellington, and is attested by numerous requests for funds recorded in the official records of the College up to her return to America. We do not know from the records which tools and materials Marian intended to buy for her laboratory, but it is very likely that among these there was a thermostat for the study of chicken embryos. In the *College Yearbook* for 1923, there is an article entitled "A pioneer institution - The Huguenot University College", we learn that, among the tools kept in the museum of the Department of Zoology there is "an incubator in which the development of the embryo in the egg" could be observed. It is plausible to assume that this incubator was one of the instruments Marian had bought for the embryology experiments that, in all likelihood, she intended to conduct in her laboratory in Wellington.

There is, however, no evidence that Marian was able to carry out any actual research experiments during her time at Huguenot College, and, indeed, no scientific publications appeared to her name in scientific journals during this period. Nonetheless, she maintained her affiliation with the American Zoological Society, a sign to feel she was still a member of the international scientific community.

It is to be assumed that the years spent in South Africa did not correspond to Marian's expectations, neither as regards her scientific activity nor for her academic position. From the documentation preserved in the Dutch Reformed Church of South Africa Archives, it seems that, among the possible reasons for



102

Department of Zoology.

DR. SHOREY.

I.—INTERMEDIATE ZOOLOGY.

LECTURES: Two periods per week: Laboratory, four periods per week.

1. The elements of anatomy, histology, physiology, and embryology, as illustrated by the frog.

2. The distinguishing characters of the following sub-kingdoms, and of the sub-divisions mentioned under each, with an elementary knowledge of the types specified:—

(a) *Protozoa*:—
Rhizopoda (*amæba*).
Mastigophora (*heteromita, euglena, volvox*).
Infusoria (*paramæcium, vorticella*).
(b) *Porifera*.
(c) *Cœlenterata*:—
Hydromedusæ (*hydra, obelia*).
Actinoza (an Actinian).
(d) *Echinodermata* (asterias).
(e) *Annulata* (*lumbricus*).
(f) *Arthropoda*:—
Crustacea (*palinurus* or *astacus*).
Insecta—the locust or cockroach, and the general characters of the chief orders of insects).

103

(g) *Mollusca*:
Gasteropoda (*helix*).
Lamellibranchiata (*unio* or *anodonta*).
(h) *Vertebrata*:—
Pisces (dogfish).
Amphibia (*rana*).
Reptilia.
Aves.
Mammalia (*lepus*).

3. The development of the chick, treated in an elementary manner.

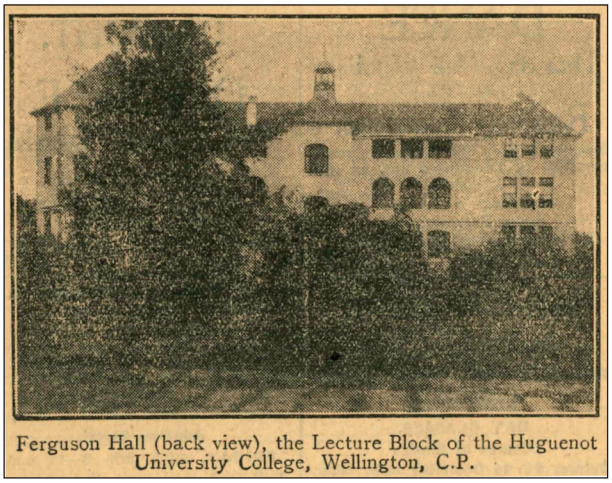
4. An elementary knowledge of Philosophical Zoology, including (1) Variation, (2) Heredity, (3) Natural Selection, (4) Degeneration and (5) Geographical Distribution.

5. Life-histories of the malarial parasite (*hæmamœba*), the liver fluke (*fasciola*), the tapeworm (*tænia*), and *phylloxera*.

II.—B.A. ZOOLOGY.

Lectures will include the following topics:—
Systematic Zoology.
Comparative Anatomy of Invertebrates and Vertebrates.
Embryology.
Cytology.
Life Histories of certain parasites of economic importance.
Philosophical Zoology, including such subjects as Evolution, Variation,

Figure 15. Two pages of the 1917 College Yearbook at the Huguenot in Wellington with the syllabus of the zoology courses taught by Marian.



Ferguson Hall (back view), the Lecture Block of the Huguenot University College, Wellington, C.P.

Figure 16. The complex of teaching buildings at Huguenot College in Wellington. This is where Marian taught her zoology courses. The image is from a newspaper clipping from 1923, which speaks of the presence, among the objects in the zoology museum, of an incubator for the study of the embryo.

disappointment, there was the fact that the official role afforded her was that of Lecturer and not the more prestigious one, which she had hoped for, of Professor.

Among the few bits information about Marian's activity as a lecturer at the Huguenot, there is a somewhat private one, indicating her sensibility and kindness. It concerns the fact that during a student excursion, with a picnic (and the possibility of swimming in the river) in Bainskloof, near Wellington, Marian had offered her pupils "a large box of chocolates".

Bina May Shorey: the tragic death of a sister sharing Marian's expectancies

Without doubt a sad event of private nature has contributed to embitter almost from beginning the period spent by Marian in South Africa, leading perhaps to a condition of depression that that might have impacted negatively on her attempts to establish a research lab at the Huguenot. This was the tragic death of Bina May, the elder sister who, as Marian, had decided to depart from the farmer life situation through an education culminating in a teaching profession. The two sisters lived parallel lives until their graduation at Brown University at the beginning of the twentieth century. After that period their lives diverge, and only Marian seems to have been able to further her university education by obtaining a PhD at Chicago University in 1909.

Undoubtedly, after the graduation at Brown, Bina May continued to work as a teacher, but now at a higher level as an advantage of her university degree. Eventually something went very wrong, as we know from a short article of *The Greenfield Recorder* of 22 November 1922 announcing her death by suicide. Bina May had been teaching at the school of Athol, MA., (a High School), but – according to the article – it was "believed that she had been mentally unbalanced for some time". The reasons for that state had to do with a "trouble with the school committee". For this – as Bina May confided to an acquaintance – "she was anticipating discharge". If that event occurred "it would be all up with her". From the article we know also that "several previous positions she had been unable to hold but a short time, and a teacher agency which had secured them for her, wrote Miss Shorey recently that it could do no more for her along this time".

The body of Bina May was found on 18 November 1916 in Lake Ellis, near Athol, after two days of a search involving several persons, including her brother, Leforest Shorey. Leforest had come to Athol from his house in Cliffondale (MA) on the morning of the 18 November (as we know from an article of the *Boston Sunday Globe* written on the same day, before the body was found). He was aware that his sister might be "mentally unbalanced temporarily". From another newspaper *The Republican Journal* of Belfast (ME)

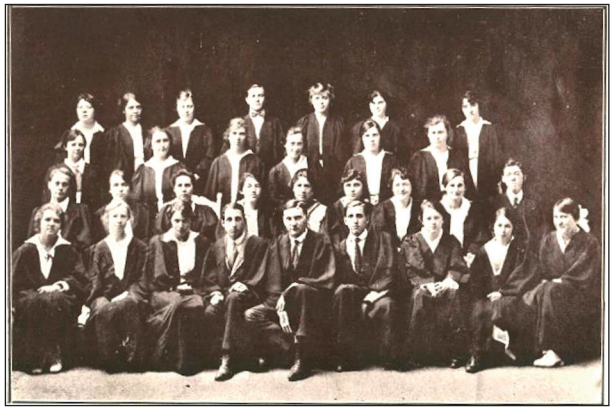
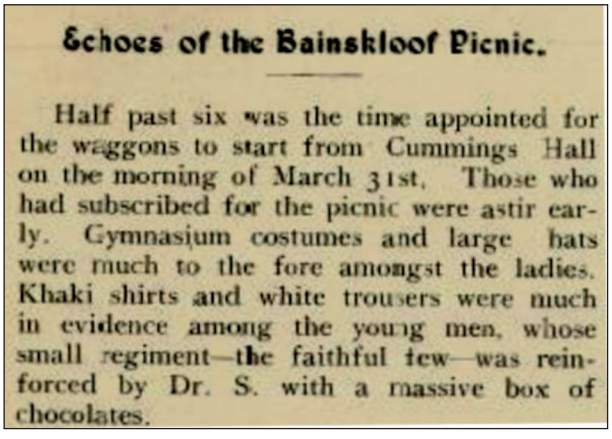


Figure 17. A group photo of the students of the "intermediate class" at the Huguenot College of Wellington, taken in 1917, in which there are almost certainly some of the students of the zoology lessons given by Marian. As one can see, at the time of Marian's tenure, Huguenot College was also attended by male students.



Echoes of the Bainskloof Picnic.

Half past six was the time appointed for the waggons to start from Cummings Hall on the morning of March 31st. Those who had subscribed for the picnic were astir early. Gymnasium costumes and large hats were much to the fore amongst the ladies. Khaki shirts and white trousers were much in evidence among the young men, whose small regiment—the faithful few—was reinforced by Dr. S. with a massive box of chocolates.

Figure 18. An excerpt from a page in Huguenot *College Yearbook for 1917*, in which, in connection with a students excursion to Bainskloof, a mountain place located not far from Wellington, it hints that Marian (referred to as "Dr. S.") offered the students a "big box of chocolates". A detail that suggests a certain concern of the teacher for her students.

which gives other details. Bina May "had been missing since Tuesday night, Nov. 14th. She had resigned four days before from her position at the Athol High School, in which she was teaching since March, because "of slight friction in the school" with her students

The melancholic return of Marian Lydia Shorey to her homeland.

Although there is not a stringent temporal and causative relation between the tragic death of Bina May and the decision of her sister to leave Wellington, it is logical to imagine that the two events were somewhat connected.

In 1916, in the application for a passport to leave the United States, Marian declared that she wanted to stay in South Africa for a period of 3-5 years. This notwithstanding, as early as June 1918, she requested a new passport for the return journey, and resigned from her role at Huguenot at the end of the academic year, in December 1918. She left South Africa in March of the following year.

The return voyage took place on a very different route than the outbound one, with a passage in Sydney (Australia) on 7 May 1919 and the arrival on the west coast of the United States, in San Francisco, on 26 May 1919 on board the liner Ventura. The departure of this ship from Sydney with, among others, a "Miss MB Shorey" [sic] was announced by the *Sydney Morning Herald* on Wednesday 7 May 1919. It is likely that, undertaking this long return voyage, Marian perhaps wanted to take advantage of the opportunity to visit remote countries and enjoy a kind of vacation.

We have little information about Marian's years in her hometown following the Ventura's arrival in San Francisco. What we do know is, however, surprising, and also very painful, because it seems to document a progressive decline in a life which, particularly after scientific work in Lillie's laboratory, appeared to herald a brilliant academic and academic career for the young scientist.

From two brief statements in a Brown University file we learn that – after having been until April 1919 at the "Wellington Huguenot College, Cape Province, So. Africa" in September 1921 Marian worked in a factory in Waterbury in Connecticut, the "Scovill Manufactures" (an industry that is still active, and that, at Marian's time, produced metal objects of various types, from buttons for clothes, to screws, ammunition and optical equipment). We also know that, in June 1921, Marian resided in Waterbury at the following address "The Cables, 45 Prospect Street".

Marian's job at Scovill was that of a clerk, and likely it was unrelated to her scientific skills (particularly in chemistry). With a return to her homeland, an apparently inexorable decline for Marian's life and career ensued, a decline that had probably started in South Africa, (and perhaps even before). Marian's life

Figure 19. A picture of Bina May Shorey (1867-1916) from the article of *The Boston Sunday Globe* of 19 November 1916.

Figure 20. The Ventura ship on which Marian Lydia Shorey embarked on her return voyage from South Africa in 1919.

prospects changed dramatically with a more or less forced adaptation to that of an ordinary worker, after the years spent as a high-profile researcher in Chicago, in Lillie's laboratory, and of university teaching in the United States and South Africa.

Nonetheless, it was difficult to imagine how Marian's existence would suddenly end on August 26, 1922, about three years after her return from South Africa. In this investigation on Shorey's life, the first clue to the particularly tragic aspect of her death came from a handwritten note affixed to the back of a register sheet with Brown University's "Graduate Records" relating to her. In this note signed by a certain "E. Hines", we read: "I understand from miss Haskell that death was due to suicide".

The proof of the painful act carried out by Marian to put an end to her days then came from two articles that appeared in newspapers of the time and from the report drawn up by the coroner. In the first article (published in the aftermath of her death – on August 27 – in a local newspaper, *The Sunday Republican* of Waterbury, we read that that the cause of death was suicide committed "by inhaling of gas". This was confirmed by the report of the coroner, Edward Harry Kirschbaum, stating that death occurred due to "illuminating gas poisoning at her own hands". In the article it is also said that, according to Marian's acquaintances, in recent times the woman (whose name is reported inaccurately "Marion", with the age also incorrect, 40 years – instead of 49) suffered from a "nervous breakdown" and showed strange behaviour over time.

Marian had carefully planned her suicide, sealing doors and windows of the house to prevent the gas escaping from her apartment, and putting her personal items in a trunk. She had then left some letters, among which, in addition to the one addressed to a brother, one destined for the newspaper in which she asked "no undue publicity be given her death".

The following day the news of Marian's tragic death (again with an imprecise name and age) appears in another local newspaper, the *Waterbury American*. Here, too, details are given that indicate the careful preparation of the tragic act, and it is suggested that the decision to end her life was the consequence of the loss of a job at the Scovill Manufactures and the difficulties in finding a new job. The importance of this article for us lies in the fact that it reports a larger part of the letter sent by Marian to the newspapers.

Here is the transcript:

If this letter is delivered to you it will be because I was found dead as a result of my own act. The world is always so surprised when a person chooses to leave it that he immediately asks everything about him, even though it might not have paid the slightest attention to him alive. I earnestly ask that I may be allowed to remain as unknown in Waterbury dead as I have been alive.

These words, full of sadness, but also of great dignity, are the main justification for the present writing and of its lingering, at times, on minor biographical details. We aim to avoid losing the track of this in-

Figure 21. An antique illustration with a view of the Scovill factory in Waterbury, the place where Marian Shorey worked for a while after returning from South Africa in 1919.

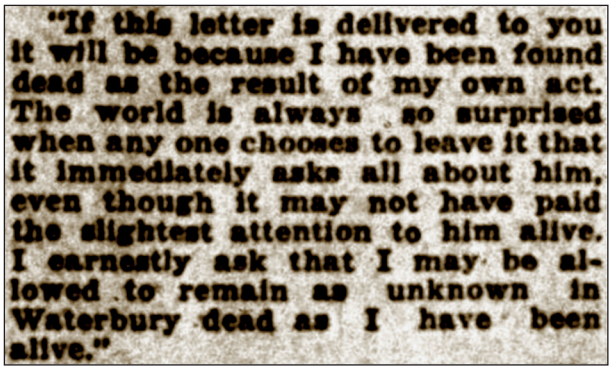

"If this letter is delivered to you it will be because I have been found dead as the result of my own act. The world is always so surprised when any one chooses to leave it that it immediately asks all about him, even though it may not have paid the slightest attention to him alive. I earnestly ask that I may be allowed to remain as unknown in Waterbury dead as I have been alive."

Figure 22. A detail of the clipping from the Waterbury American dated 28 August 1922, with the words of the letter in which Maria asked for silence, from the press, on her tragic act. Both Marian and her sister Bina May took their life at the age of 49 years.

telligent and unfortunate woman, who – with her extraordinary experiments in 1909 – set in motion a path of research that would, many years later, lead to one of the greatest discoveries in the biology of Twentieth century.

One final notation; if the reporter of the *Waterbury American* has accurately transcribed the words of Marian's letter, then, in the absence of other personal letters and writings (so far undiscovered after an intense search) the above lines are the only words that remain of an unscientific text written by Marian Lydia Shorey herself. She was like a shooting star that shows itself to us only by disappearing.

Acknowledgements

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References

1. Piccolino M. Youthfulness, Vocations, and First Experiments of Rita Levi-Montalcini, scientist. First part: the difficult choice of a graduate in medicine. Conf Cephalal et Neurol. 2021; 31:1-8.
2. Piccolino M. Rita Levi-Montalcini's first intellectual emigration and her research in the laboratory "à la Robinson Crusoe": the letters from Brussels and a "Wiggish" recollection Conf Cephalal et Neurol. 2021; 31:1-27.
3. Piccolino M. (ed.)) Rita Levi-Montalcini e il suo Maestro. Una grande avventura scientifica nelle neuroscienze del Novecento. Pisa: ETS 2021.
4. Levi-Montalcini R. The Nerve Growth Factor: thirty years later. The Nobel Lectures. https://www.nobelprize.org/uploads/2018/06/levi-montalcini-lecture.pdf, 1986.
5. Shorey ML. The effect of the destruction of peripheral areas on the differentiation of the neuroblasts. J Exp Zoöl 1909; 8: 25-63.
6. Shorey ML. Study of the differentiation of neuroblasts in artificial culture media. J Exp Zoöl 1911; 10:85-93.
7. Levi-Montalcini R. *Elogio dell'imperfezione*. Milano: Garzanti 1987.
8. Lillie FR. The Development of the Chick. An Introduction to Embryology. New York: Holt 1908.
9. Detwiler SR. The effects of bilateral extirpation of the anterior limb rudiments in *Amblystoma* embryos. J Comp Neur 1924; 37:1-14.
10. Detwiler SR Experimental studies on morphogenesis in the nervous system. Quart Review Biol 1926; 1:61-86.
11. Hamburger V. The effects of wing bud extirpation on the development of the central nervous system in chick embryos. J Exp Zoöl 1934; 68:449–494.
12. Allen GE, J. W. Baker. Biology: scientific process and social issues. Bethesda, Md: Fitzgerald Science Press 2001
13. Allen GE. A pact with the embryo: Viktor Hamburger, holistic and mechanistic philosophy in the development of neuroembryology, 1927-1955. J Hist Biol 2004; 37:421–475.
14. Modiano P. Dora Bruder. Paris, Gallimard 1997.
15. Wiggin, Ruby Crosby. 1964. Albion on the narrow gauge. Clinton, ME, 1964 [publisher not identified].
16. Annual Report of the Municipal Officers and Supervisor of Schools, of the Town of Albion, for the Year Ending March, 7th, 1890, Maine Town Documents. 1150. Albion, ME, 1890. Digital copy downloaded from the following webpage: https://digitalcommons.library.umaine.edu/

townddocs/1150/
17. Catalogue and Circular of the Eastern State Normal School at Castine, Maine, 1894, Castine, ME, Sprague and Son, Augusta, ME, 1894.
18. Lake Placid Conference on Home Economics, Proceedings of the Seventh Annual Conference of Home Economics". Lake Placid Club. Essex Co. NY 1906.
19. Gilchrist BB. The life of Mary Lyon. Boston and New York, Houghton Mifflin Company, The University Press Cambridge 1910.
20. Stenghel, HO. The Story of Mary Lyon. Newark and New York: Barse and Hopkins 1922.
21. Douglas WM., Murray Annie: Andrew Murray and his Message… London, Edinburgh: Oliphants 1926.
22. Duff SE. Head, Heart, and Hand: the Huguenot Seminary and College and the Construction of Middle Class Afrikaner Femininity, 1873-1910. Thesis (MA). History. University of Stellenbosch (2006).
23. Duff S. E. From New Women to College Girls at the Huguenot College. 1895-1910. Historia 2006); 51:1-27.
24. Duff S. E. (2015). Changing Childhoods in the Cape Colony: Dutch Reformed Church Evangelicalism and Colonial Childhood, 1860-1895. London: Palgrave Macmillan, 2015.
25. Laurenzi E. Fili della trasmissione: il progetto delle donne De Viti de Marco-Starace nel Salento del Novecento. Lecce: Grifo (Cavallino) 2019.

Correspondence:
Marco Piccolino
Centre of Neurosciences of the University of Ferrara,
Ferrara, Italy.
E-mail: marco.piccolino@yahoo.it

La diagnosi di malattia di Alzheimer: stato dell'arte e attuali controversie

Alfredo Costa[1,2], Giulia Perini[1,2], Camillo Imbimbo[1] Lucia Scanu[1], Matteo Cotta Ramusino[2]

[1]Dipartimento di Scienze del Sistema Nervoso e del Comportamento, Università di Pavia; [2]Unità Complessa Neurologia del Comportamento e Centro Disturbi Cognitivi e Demenze (CDCD), Istituto Neurologico Nazionale IRCCS Mondino, Pavia

Riassunto. Il capitolo della diagnosi di malattia di Alzheimer (AD), sostanzialmente invariato dai primi anni '80, ha conosciuto negli ultimi tempi una ripresa dell'interesse scientifico e clinico sulla base di acquisizioni via via crescenti, e rappresenta oggi uno degli ambiti di ricerca di maggior sviluppo della Neurologia. In questa rassegna sono riportati gli avanzamenti più recenti, principalmente basati sull'utilizzo dei marcatori neurobiologici di malattia, e gli aspetti attualmente più dibattuti, quali il loro impatto e il loro valore diagnostico incrementale sulla diagnosi precoce nei casi tipici, e in quelli caratterizzati da comorbidità o da associazione con la patologia vascolare cerebrale (forme miste).

Parole chiave: Alzheimer, diagnosi, biomarcatori, demenza mista.

The diagnosis of Alzheimer's disease: an update and current controversies

Abstract. The chapter of the diagnosis of Alzheimer's disease (AD), almost unchanged since the early 80's, has been recognizing over the last years a revival of scientific and clinical interest, following increasing advances, and currently represents one of the main developing fields of neurological research. In this review we report the most recent evidence in the field, mainly based on the use of neurobiological markers of disease, as well as the current most debated issues, such as the impact of markers on the diagnostic workup and their incremental diagnostic value with respect to early diagnosis in typical cases and in those characterized by comorbidities or association with brain vascular pathology (mixed forms).

Key words: Alzheimer, diagnosis, biomarkers, mixed dementia.

La malattia di Alzheimer (*Alzheimer's disease, AD*) è una patologia degenerativa del sistema nervoso centrale che interessa nel 95% dei casi individui oltre i 65 anni, e che porta al decesso in media nell'arco di 10 anni, benché si stia da tempo assistendo ad un allungamento della sopravvivenza, legato al miglioramento delle terapie sintomatiche e alla maggiore attenzione rivolta alle complicanze della malattia. Sostanzialmente invariato sin dai primi anni '80, il capitolo della diagnosi di AD ha conosciuto negli ultimi anni una ripresa dell'interesse scientifico e clinico sulla base di acquisizioni via via crescenti, e rappresenta oggi uno degli ambiti di ricerca di maggior sviluppo della Neurologia.

Quadri clinici di AD

La diagnosi di AD non può ovviamente prescindere dal quadro clinico del paziente (dati anamnestici, fenotipo). La presentazione classica dell'AD è caratterizzata da un precoce e significativo disturbo della memoria episodica, con evidenza di una sindrome amnestica di tipo ippocampale. Essa consiste in par-

ticolare in un difetto nel *recall* (richiamo) che non migliora significativamente o non si normalizza con il *cueing* (suggerimento semantico); ad esempio, il Free and Cued Recall Test (FCRT), che valuta proprio questi aspetti, è uno strumento che sembra in grado di distinguere, in modo sensibile e specifico, il difetto nei processi di codifica ed apprendimento dell'AD da quello presente in altre condizioni fisiologiche o patologiche, quali invecchiamento cerebrale, depressione maggiore, demenza fronto-temporale e demenze sottocorticali (1). Al disturbo di memoria si associa di solito, da subito o in tempi successivi, l'interessamento di altri domini cognitivi: deficit di memoria semantica, sequenziale impoverimento delle funzioni attentive ed esecutive, del linguaggio, dell'orientamento, delle abilità visuo-spaziali e della prassia. Il coinvolgimento di questi domini cognitivi è coerente con l'estensione delle lesioni patognomoniche della malattia dalle regioni ippocampale e meso-limbica a quelle neocorticali. La graduale comparsa di un deficit multisettoriale determina una progressiva compromissione della capacità di adempiere alle attività abituali della vita quotidiana, riducendo l'autonomia individuale e rendendo necessaria l'assistenza da parte dei *caregiver.* Alterazioni della condotta, comportamenti sessuali inappropriati, disturbi dell'umore, allucinazioni, manifestazioni dispercettive, anomalie dell'ideazione fino al delirio, agitazione ed aggressività (verbale o fisica), depressione o apatia, sono la principale fonte di carico per il caregiver, e un'importante causa di istituzionalizzazione di questi pazienti (2). Questi aspetti, riunificati nel termine BPSD (*behavioral and psychological symptoms of dementia*), sono riscontrabili tanto nei pazienti con disturbi cognitivi lievi (MCI) che in quelli con forme severe di demenza. Nelle fasi terminali, con la diffusione dell'atrofia cerebrale, insorgono anche alterazioni del movimento, difficoltà nella masticazione, disfagia, difficoltà nel mantenere la stazione eretta o il tronco; sono possibili crisi epilettiche, ipertono, mioclonie ed incontinenza sfinterica. Infine, il decesso avviene di solito a causa di patologie intercorrenti, in particolare infezioni delle vie aeree, delle vie urinarie o sepsi a partenza da ulcere da decubito.

Nel 6-14% dei casi, tuttavia, la presentazione dell' AD differisce dalla forma amnestica classica, configurando una forma atipica (3). Ciascuna di queste forme si presenta spesso con una relativa conservazione della memoria e con un fenotipo clinico che dipende dalla sede topografica del danno cerebrale, come testimoniato dall'atrofia corticale e dalla riduzione dell'attività metabolica riscontrabili al neuroimaging. Le forme atipiche presentano generalmente un esordio più precoce dell'AD amnestica e si manifestano in tre forme principali: una variante posteriore, una logopenica e una comportamentale. La *variante posteriore*, caratterizzata appunto da atrofia corticale posteriore (PCA) (4), comprende una serie di segni e sintomi che configurano due sottotipi: uno occipito-temporale, con prevalente disturbo nel riconoscimento di oggetti, simboli, parole o volti, e un sottotipo biparietale, con prevalente disfunzione visuo-spaziale, con aspetti propri della sindrome di Gerstmann o Balint (aprassia o neglect). La *variante logopenica* di AD, si presenta come afasia primaria progressiva (PPA) ad impronta logopenica, ovvero come un disturbo progressivo del richiamo di singoli vocaboli e della ripetizione di frasi, in un contesto di abilità semantiche e sintattiche conservate (5). Infine, la *variante frontale* di AD si presenta come una forma prevalentemente comportamentale, con apatia progressiva o disinibizione e stereotipie, o con prevalente alterazione delle funzioni esecutive (6). Uno studio clinico e patologico (7) condotto su pazienti con variante frontale di AD ha dimostrato che il riconoscimento di questa forma non è solo basato su

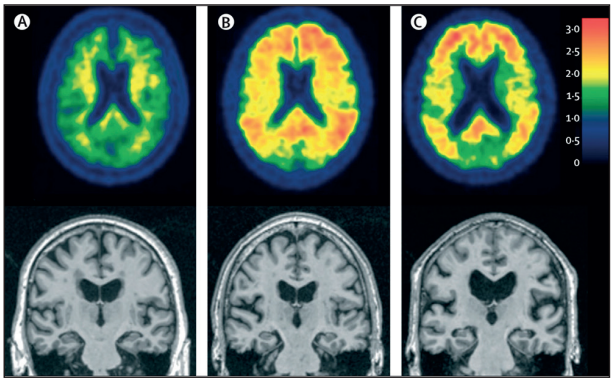

Figure 1. PET-amiloide con PiB in vari stadi di AD: A) soggetto cognitivamente integro che non mostra accumulo di beta-amiloide alla PET con PiB né atrofia alla RM. B) soggetto cognitivamente integro senza evidenza di atrofia alla RM ma con significativa deposizione di Aβ alla PET . C) paziente con demenza e diagnosi di AD con uno studio PET positivo per amiloide e atrofia alla RM (19).

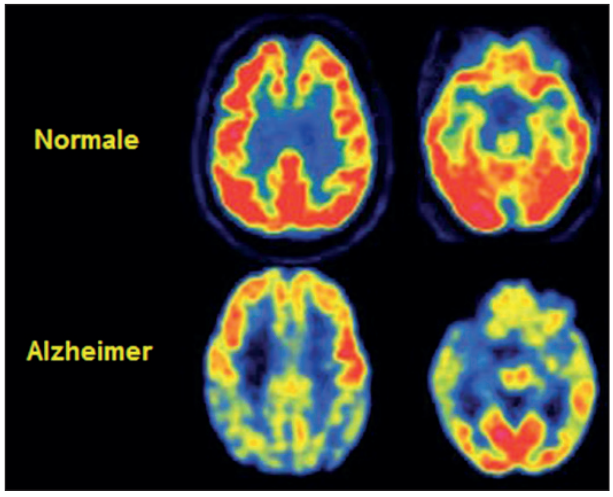

Figure 2. Immagini FDG-PET di un soggetto normale di controllo e di un paziente con AD. Si apprezza un quadro di severo ipometabolismo (regioni corticali in giallo e blu) nella corteccia associativa e limbica (lobi parietale postero-mediale e laterale, e temporale laterale e mediale) (23).

elementi clinico-osservazionali, ma anche su evidenze neuropatologiche, in quanto questi soggetti presentano un maggior numero di lesioni caratteristiche (in particolare gomitoli neurofibrillari) a livello dei lobi frontali. Distinguere la variante comportamentale dell'AD da quella della degenerazione lobare fronto-temporale (FTLD) non è semplice, neanche con l'ausilio di batterie di test neuropsicologici validati. Nell'AD sembrano tuttavia prevalere disinibizione, irritabilità, agitazione, allucinazioni e deliri, mentre nella FTLD prevalgono modificazioni più profonde che alterano gradualmente personalità e carattere, oltre a un coinvolgimento significativo della critica e del *problem solving* (6). Evidenze neuropatologiche ottenute da pazienti con sindromi corticali focali progressive hanno dimostrato come la AD, definita da criteri anatomopatologici, possa presentarsi in modo alquanto variabile, con aspetti fenotipici atipici, diversi da quelli classicamente riconosciuti: atrofia corticale posteriore (100% AD), sindrome

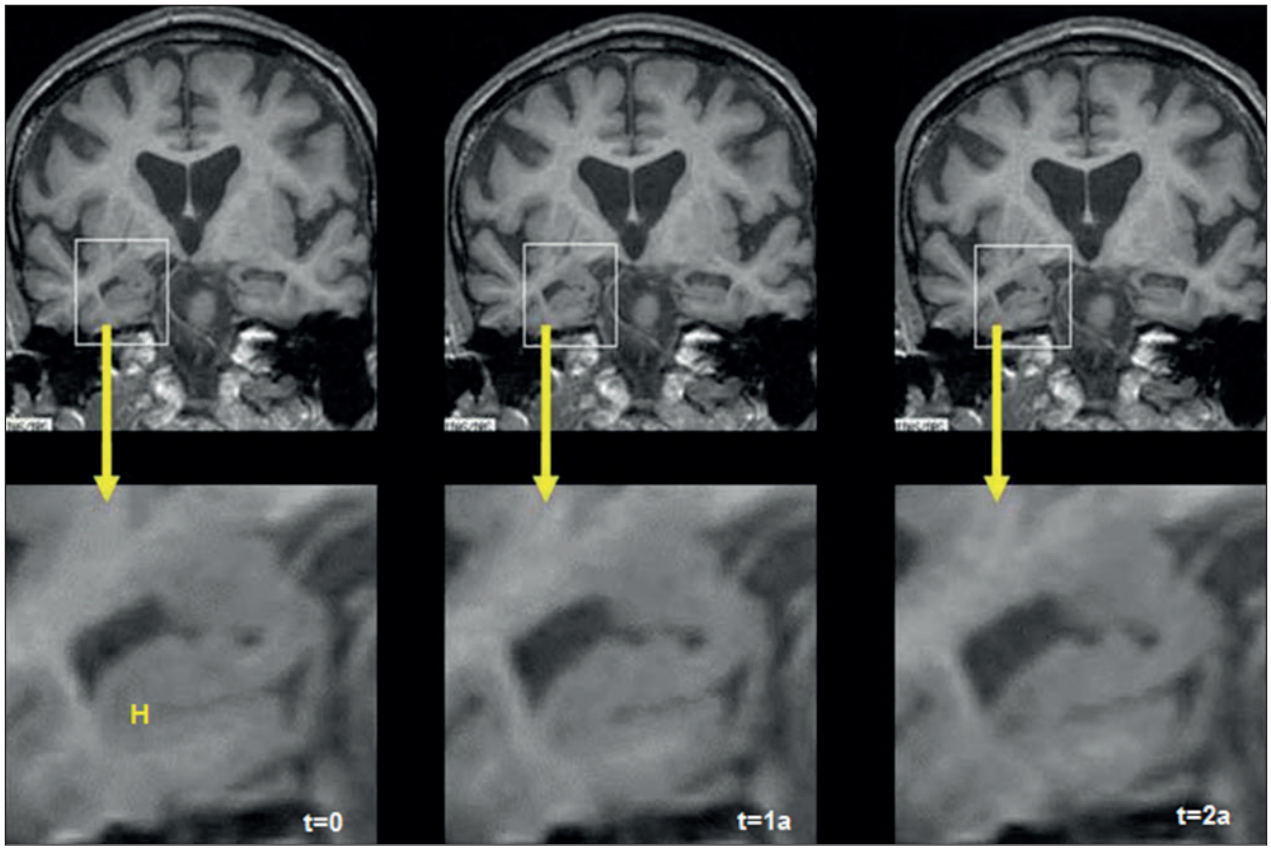

Figure 3. Sezioni RM coronali T1-pesate di un soggetto con diagnosi autoptica di AD che mostrano la progressione dell'atrofia ippocampale (H) dal momento dei primi sintomi cognitivi (a sinistra) e ad intervalli di un anno fino alla diagnosi clinica (a destra) (23).

cortico-basale (50% AD), demenza fronto-temporale variante comportamentale (7.1% AD), afasia primaria non fluente (44.1% AD), afasia mista (71.4% AD), demenza semantica (10% AD) (8).

Il fenotipo clinico dell'AD può includere, oltre alle alterazioni cognitive, anche disturbi del movimento, per lo più di tipo extrapiramidale, in una percentuale variabile dal 20 al 50% (9). Si tratta generalmente di manifestazioni di grado lieve-moderato, non indotte dall'assunzione di farmaci antipsicotici (tipici o atipici); quelle più frequentemente riportate sono ipomimia, disartria e bradilalia, bradicinesia, rigidità, disturbi della marcia ed instabilità posturale. La presenza di disturbi del movimento sembra tuttavia giocare un ruolo in termini di sopravvivenza; è stato infatti osservato che i pazienti con un quadro di compromissione extrapiramidale e/o con evidenza di corpi di Lewy all'esame autoptico sono caratterizzati da un'aspettativa di vita dimezzata rispetto ai pazienti con soli disturbi cognitivi (10). Infine, in forme familiari di AD, legate ad esempio alla mutazione dei geni della presenilina 1 e 2 (PSEN 1 e 2), sono descritte altre manifestazioni, quali mioclonie, crisi epilettiche, atassia, paraparesi spastica, distonie.

I biomarcatori

Gli aspetti clinici e le alterazioni del quadro cognitivo rilevabili ai test neuropsicologici sono ovviamente fondamentali ai fini dell'inquadramento diagnostico. I biomarker, o marcatori biologici, sono indicatori che riflettono le modificazioni metaboliche, citologiche o morfo-funzionali tissutali che avvengono nel corso del processo fisiopatologico di una data malattia. La loro utilità nella diagnostica, anche dell'AD, sta nel fatto che essi sono evidenziabili e misurabili *in vivo*, generalmente in modo non invasivo o mini-invasivo, e sono ripetibili.

Marcatori nel liquido cerebrospinale

Nel caso dell'AD, i livelli di $A\beta_{42}$, proteina tau totale (t-tau) e proteina tau fosforilata (p-tau) nel liquido cerebrospinale riflettono i processi metabolici che si verificano nel corso della "cascata" dell'amiloide, e sono quindi essere utili per la caratterizzazione delle fasi precliniche di malattia e per la formulazione di una diagnosi precoce. I livelli di $A\beta_{42}$ nei pazienti sono diminuiti e presentano una correlazione inversa con il carico di amiloide nell'encefalo: maggiore la deposizione e quindi il sequestro in placche senili, minore il livello di proteina solubile circolante nel liquor. I livelli di t-tau e p-tau sono invece aumentati, e correlano con la quantità di gomitoli neurofibrillari e con l'entità della neurodegenerazione. La misurazione di questi indici può essere utilizzata per discriminare i pazienti con AD da soggetti non dementi di pari età e da pazienti affetti da altre condizioni morbose, quali il disturbo depressivo maggiore e la malattia di Parkinson (11). I livelli di p-tau liquorale, in particolare, aiutano nella diagnosi differenziale tra AD e altre forme di demenza, ad esempio quella della malattia a corpi diffusi di Lewy. Tuttavia, il potenziale diagnostico dei biomarker liquorali non appare essere ottimale a causa di un'ampia sovrapposizione, come dimostrato all'esame autoptico, tra AD, malattia a corpi diffusi di Lewy e demenza vascolare; tale fenomeno preclude la possibilità di ottenere una specificità e una sensibilità del 100%. I biomarker liquorali sembrano invece possedere un elevato valore predittivo nell'identificare le forme prodromiche (*prodromal AD)* tra i soggetti con MCI. La combinazione di tutti e tre gli indicatori (t-tau, p-tau e $A\beta_{42}$) mostra inoltre una sensibilità del 95% nel riconoscere i *prodromal AD* e nel predire la velocità di progressione verso l'AD conclamata (12). Con il termine di *AD preclinico* si fa riferimento, invece, ad individui cognitivamente integri portatori di un'iniziale patologia tipo AD, ma non abbastanza severa da esprimersi con disturbi cognitivi. Uno studio di popolazione (13) ha evidenziato una significativa riduzione dei livelli liquorali di $A\beta_{42}$ in soggetti anziani cognitivamente normali che hanno successivamente sviluppato AD; inoltre, in questi stessi soggetti, il rapporto $A\beta_{42}$/tau si è rivelato un forte predittore di declino cognitivo nei successivi due anni di osservazione. Livelli elevati di tau si ritrovano invece in individui che presentano già un declino cognitivo, MCI o demenza, e correlano in parte con il grado di atrofia corticale cerebrale (14). Queste osservazioni suggeriscono che l'aggregazione e deposizione di Aβ sono associate con la fase preclinica della malattia, mentre le modificazioni nei livelli di tau

liquorale e l'atrofia cerebrale sono eventi successivi, che si verificano in coincidenza o appena prima dell'inizio del declino cognitivo.

Ai fini dell'impiego di questi marcatori nella diagnosi di AD, va considerato che un fenotipo suggestivo di malattia (sindrome amnestica del tipo ippocampale) cui si accompagni una semplice riduzione dei livelli liquorali di amiloide non può essere considerato specifico di AD, poichè il dato può riscontrarsi in diverse altre condizioni neurodegenerative (ad es. LBD, angiopatia amiloide). Analogamente, una sindrome amnestica suggestive di AD, con isolato riscontro di aumento della tau liquorale, non è sufficiente per una definizione diagnostica, potendosi osservare anche in forme cliniche più rare come ad esempio presentazioni atipiche di FTLD. L'indicazione più diffusamente riconosciuta oggi nella comunità scientifica è pertanto quella di considerare, ai fini della diagnosi di AD, la combinazione nel liquor di entrambe le alterazioni (beta-amiloide e tau).

Molte altre variabili liquorali sono state indagate negli anni con possibile valore di biomarcatori, ma con risultati non conclusivi. BACE1 può essere misurata nel liquor, e la sua concentrazione ed attività sono aumentate in AD, specialmente in casi prodromici (15). L'impiego di anticorpi monoclonali nei dosaggi ELISA ha permesso di rilevare alti livelli di oligomeri di Aβ (16), che sembrano associarsi ad inibizione della *long-term potentiation* (LTP) a livello ippocampale e quindi al disturbo della memoria. $A\beta_{40}$ è l'isoforma di Aβ più abbondante nel liquor, anche se non vi è alcuna significativa modificazione dei suoi livelli liquorali in AD, né alcuna correlazione con il carico di amiloide. Tuttavia è osservabile una riduzione del rapporto $A\beta_{42}$/ $A\beta_{40}$ che è più pronunciata della riduzione della sola $A\beta_{42}$ (17). Altri peptidi Aβ, troncati in siti carbossi-terminali ($A\beta_{37}$, $A\beta_{38}$ e $A\beta_{39}$) sono stati identificati: il riscontro di i livelli aumentati di questi peptidi e il loro rapporto con $A\beta_{42}$ potrebbero, secondo alcuni autori, incrementare l'accuratezza diagnostica dei biomarker comunemente usati (18).

Marcatori di neuroimaging

Il primo tracciante specifico per l'amiloide ad essere sviluppato è stato il PIB (Pittsburgh Compound B), un derivato ^{11}C del colorante istologico tioflavina-T:. Esso si lega selettivamente alla forma fibrillare dell'Aβ sia nel parenchima che nei vasi cerebrali, e correla direttamente con la presenza di placche neuritiche all'autopsia e inversamente con i livelli liquorali di $A\beta_{42}$. Bassi livelli di $A\beta_{42}$ sono stati tuttavia riscontrati

Tabella 1. - Evoluzione dei requisiti per la diagnosi di AD, attraverso le proposte dei vari gruppi di lavoro.

	NINCDS 1984	**IWG 2007**	**IWG 2010**	**NIA-AA 2011**	**IWG 2014**	**NIA-AA 2018**
Requisiti clinici	Deficit in due domini cognitivi	- Sindrome amnestica del tipo ippocampale	- Sindrome amnestica del tipo ippocampale - Forme atipiche (PCA, logopenica, frontale/ comportamentale)	- MCI (amnestico o non amnestico) - Demenza	- Sindrome amnestica del tipo ippocampale - Forme atipiche (PCA, logopenica, frontale/ comportamentale)	NESSUNO
Requisiti biologici	NESSUNO	- biomarcatori LCS - Atrofia alla RM - Ipometabolismo alla PFDG-PET - Positività alla PET amiloide	- marcatori fisiopatologici (LCS, PET amiloide)	- marcatori di amiloide (amiloide in LCS, PET amiloide) - marcatori di neurodegenerazione (tau e p-tau in LCS,RM, FDG-PET)	- amiloide in LCS OPPURE positività alla PET amiloide	- marcatori di amiloide (LCS, PET) E marcatori di tau (LCS, PET)

NINCDS-ADRDA= National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association
IWG= International Working Group
NIA-AA= National Institute of Aging - Alzheimer Association

anche in individui PIB-negativi (14). Ciò può essere spiegato con l'aggregazione di Aβ in placche diffuse (PIB-negative) o con l'accumulo di oligomeri di Aβ nel parenchima cerebrale prima che abbia luogo la deposizione di Aβ fibrillare (PIB-positiva). Florbetaben, florbetapir e flutemetamol sono sonde marcate con ^{18}F che possiedono caratteristiche di legame simili al PIB ma con emivita più lunga. Nell'AD si osserva un aumento della captazione corticale globale e regionale (Fig.1), in particolare nel cingolo, e nella corteccia, temporale, frontale e parietale. Circa l'85-90% dei casi diagnosticati come demenza di AD presenta una PET positiva per accumulo di amiloide. Inoltre, circa il 90% degli MCI positivi alla PET progredisce a demenza franca tipo AD durante il follow up. Anche vari traccianti tau-specifici sono stati sviluppati negli ultimi anni: tra questi, il THK5117 ha mostrato un'alta affinità e selettività di legame con la patologia tau. L'alta ritenzione del tracciante in pazienti con AD ha permesso un'eccellente distinzione dai soggetti sani dove la captazione è bassa (19). Inoltre la ritenzione del tracciante ripercorre in vivo la diffusione temporale della taupatia, così come messo in evidenza dagli studi autoptici di Braak (20). Pazienti con *prodromal AD* o con demenza da AD mostrano una distribuzione di THK5117 diffusa alle aree isocorticali, oltre a quelle limbiche, senza che vi sia una differenza statisticamente significativa tra i due gruppi. Sembra quindi che la propagazione isocorticale della patologia tau preceda lo sviluppo di demenza e sia di entità maggiore nei soggetti con demenza rispetto ai *prodromal AD*. La captazione striatale di THK5117 è stata osservata sia in controlli sani che in soggetti affetti; tuttavia la localizzazione del tracciante a livello del putamen ha consentito una buona discriminazione tra i due gruppi. I pattern di distribuzione corticali e sottocorticali di THK5117 consentono di distinguere i soggetti con MCI o demenza da AD da individui affetti da altre taupatie (21), benchè manchi una correlazione topografica tra sindrome clinica e distribuzione cerebrale di tau.

Il [^{18}F]fluorodesossiglucosio è un tracciante che fornisce una misura del consumo regionale di glucosio da parte del tessuto cerebrale, e quindi una misura diretta della sua attività metabolica. Misurando in campioni autoptici di cervello di babbuino i livelli di sinaptofisina, una proteina contenuta nelle vescicole sinaptiche, è stato possibile stabilire una correlazione positiva tra il consumo di glucosio e l'attività sinaptica dei neuroni glutammatergici (22). Nel contesto dell'AD, una diminuita captazione di FDG è indica una funzionalità sinaptica ridotta. I pazienti con AD mostrano un tipico pattern di ridotta captazione in corrispondenza delle regioni temporo-parietali laterali, nel cingolo posteriore e precuneo, oltre che dell'ippocampo e della corteccia temporo-mesiale (23) (Fig.2). Un interessamento bilaterale asimmetrico è comune negli stadi precoci, mentre nelle fasi avanzate si può osservare un coinvolgimento delle aree associative prefrontali e infine delle aree corticali primarie. Le regioni inizialmente interessate dall'ipometabolismo sono anatomicamente e funzionalmente interconnesse e formano parte del "*default mode network*" (DMN), una rete di aree cerebrali maggiormente attive durante il riposo (*resting state*) che vanno incontro a riduzione dell'attività (deattivazione) quando il cervello è chiamato ad eseguire dei compiti. Queste aree svolgerebbero un'attività "di fondo" destinata ad un lavoro mentale principalmente introspettivo e di elaborazione di piani, progetti ed azioni (24). Studi con PET-FDG hanno evidenziato un differente coinvolgimento di specifici network in ciascuna variante clinica di AD (25). Nella PCA, ad esempio, si è osservato un maggior coinvolgimento delle regioni occipitale laterale e temporale postero-inferiore (aree visive associative), mentre nella variante logopenica l'ipometabolismo è prevalente nella corteccia temporo-parietale sinistra (area del linguaggio). Pazienti con variante frontale di AD presentano invece una significativa riduzione del metabolismo nelle regioni orbito-frontali e fronto-mesiali bilateralmente, pattern che li distingue sia da quelli con altre forme di AD, che da quelli affetti da FTD, nei quali si riscontra una ridotta captazione di FDG anche nelle aree frontali laterale e superiore (26).

L'atrofia cerebrale progressiva è un aspetto caratteristico della neurodegenerazione che può essere evidenziato in vivo con la risonanza magnetica (RM) strutturale. Il maggiore contributo all'atrofia è dato dalla perdita neuronale e dendritica; i volumi in RM mostrano infatti una stretta correlazione con la conta neuronale all'autopsia (27). L'AD è caratterizzata da un esordio insidioso dell'atrofia, che dapprima si man-

ifesta nel lobo temporale mesiale (Fig.3). La corteccia entorinale è tipicamente la prima sede colpita, seguita a breve latenza da ippocampo, amigdala e paraippocampo (28). Altre strutture vengono poi coinvolte, dal cingolo posteriore alla neocorteccia temporale e alla altre aree associative, in genere con un pattern simmetrico. Questa sequenza di progressione riflette molto bene gli stadi di diffusione della patologia tau a livello istopatologico, descritti da Braak. In una significativa minoranza di casi di AD il pattern di atrofia concorda con il fenotipo clinico (atrofia temporale sinistra nella variante logopenica e atrofia occipitale nella PCA). Risulta sempre più chiaro che al momento della diagnosi di AD l'atrofia sia già instaurata: studi longitudinali di RM su pazienti inizialmente asintomatici che in seguito hanno sviluppato AD hanno osservato volumi ippocampali già ridotti di circa il 10% tre anni prima della diagnosi (29). Misure volumetriche del tessuto cerebrale mostrano una forte correlazione tra il grado di atrofia e la severità del decadimento cognitivo lungo tutto lo spettro di malattia, dalla fase asintomatica alla demenza conclamata. Distinguere i soggetti con MCI che evolveranno verso l'AD da quelli che rimarranno in una condizione stazionaria è un compito difficile: l'atrofia temporo-mesiale è un significativo predittore di progressione, con sensibilità e specificità del 50-70% (30). L'atrofia ippocampale tende ad essere più severa in AD rispetto ad altre forme di demenza, anche se è un reperto riscontrabile anche nella malattia a corpi diffusi di Lewy e nella demenza vascolare. L'utilizzo di specifiche scale, dedicate sia all'atrofia del lobo temporale (MTA) che a quella delle aree cerebrali posteriori (PA) sulla base dell'imaging, è di grande aiuto nella diagnosi; sono attualmente disponibili valori normativi età-specifici anche per la popolazione italiana (31).

Anche nella demenza fronto-temporale si può osservare una riduzione volumetrica della regione ippocampale, ma a differenza dell'AD l'atrofia è più pronunciata a sede anteriore ed è asimmetrica, con tassi di progressione più ampi (32). I vantaggi dell'impiego della RM rispetto ad altre tecniche di imaging molecolare sono la sua disponibilità sul territorio, la sicurezza per il paziente e il minor costo.

Un modello di progressione temporale dei biomarker molto noto agli addetti ai lavori è stato proposto da Jack e Holtzman (33) per meglio comprendere l'evoluzione della patologia e poter impiegare efficacemente questi indicatori nel percorso diagnostico. Nell'AD sporadica sono comunemente presenti alterazioni neurodegenerative correlate all'invecchiamento fisiologico, a patologie non-AD o ad entrambi. Benché numerose evidenze identifichino nella deposizione di amiloide il *core* o *primum movens* del processo fisiopatologico dell'AD, altri dati supportano l'idea che il declino cognitivo e i marcatori di neurodegenerazione possano precedere quell'evento. Studi autoptici hanno infatti dimostrato, in primo luogo, che la maggior parte della popolazione generale presenta un certo grado di taupatia temporo-mesiale in assenza di placche di amiloide, lasciando supporre che ciò valga anche per molti individui che eventualmente sviluppano AD (34). Inoltre, è stato osservato in studi longitudinali come la RM strutturale e la PET-FDG (marcatori di neurodegenerazione) possano modificarsi precocemente in soggetti in età avanzata, prima che si possa evidenziare la deposizione di amiloide (35). Ciò dimostra che entrambi i modelli fisiopatologici che prevedono come primo evento la deposizione di amiloide oppure la neurodegenerazione sono plausibili nella fase preclinica di AD. La neurodegenerazione tau-dipendente ed età-correlata interessa quindi inizialmente il tronco encefalico e la regione temporale mesiale; i livelli dei rispettivi biomarker (tau liquorale, RM e PET-FDG) possono risultare già alterati o cadere al di sotto della soglia di significatività. Segue la deposizione di amiloide, che si diffonde indipendentemente alle aree associative neocorticali. L'amiloidosi può successivamente trasformare la taupatia temporo-mesiale lentamente progressiva in un processo aggressivo, inducendone la diffusione verso la neocorteccia. A questo punto, uno o più biomarker di neurodegenerazione si alterano, e i sintomi clinici seguono questo andamento, con un declino cognitivo tanto più severo quanto più diffusi sono il processo patologico e l'atrofia corticale.

Recenti sviluppi della diagnosi di AD

La diagnosi di demenza è basata sui criteri del Diagnostic and Statistical Manual Disorders (DSM-V) che richiedono la presenza di un disturbo della memoria e di almeno un altro dominio cognitivo, entrambi

di entità tale da interferire con il funzionamento sociale, lavorativo o con le attività della vita quotidiana. I primi criteri diagnostici per l'AD, i criteri NINCDS-ADRDA (36), codificati da McKhann e colleghi nel 1984, distinguevano tre forme cliniche (Alzheimer probabile, possibile e definito), sulla base di un concetto probabilistico. La presenza di un peggioramento progressivo della memoria e di un'altra funzione cognitiva, l'esordio tra i 40 e i 90 anni (più spesso oltre i 65 anni), l'assenza di alterazioni di coscienza e di altri disordini sistemici o cerebrali in grado di giustificare il decadimento, definiva *l'AD probabile*. In presenza di eventuali atipie nella storia naturale della malattia (esordio, presentazione clinica o decorso) oppure dei disordini in grado di produrre demenza, la diagnosi di AD doveva essere considerata solo *possibile*. La certezza della diagnosi (*AD definita*) era invece garantita solo dall'esame istopatologico e dalla presenza delle lesioni caratteristiche (gomitoli neurofibrillari e placche senili). Tale approccio clinico-neuropatologico, e l'assenza, in quegli anni, di criteri clinici e biologici per il riconoscimento delle altre demenze, ha mostrato di possedere una bassa specificità diagnostica per AD (23-88%) (37). Molte altre forme, quali la demenza fronto-temporale, la degenerazione corticobasale CBD), la demenza a corpi di Lewy e la demenza vascolare, potevano infatti soddisfare i criteri di NINCDS-ADRDA. Nel corso degli ultimi 15 anni, la maggiore precisione nella definizione istopatologica, la migliore comprensione dei processi fisiopatologici sottesi alla malattia, e la disponibilità in vivo dei biomarker di patologia hanno permesso una migliore caratterizzazione della storia naturale di malattia e hanno promosso ripetuti tentativi di revisione diagnostica e nosografica. Il primo di questi, effettuato dall' International Working Group (IWG) nel 2007, ha rappresentato un approccio realmente innovativo nel considerare l'AD come entità nosografica clinico-biologica (38). Basato sia sulle evidenze biologiche (biomarcatori) che sulle caratteristiche fenotipiche dei pazienti, esso ha consentito di ampliare il *continnum* clinico dell'AD da una fase prodromica ad una di demenza conclamata. In pratica, in base ai criteri proposti, l'AD poteva essere riconosciuto *in vivo*, indipendentemente dal grado di compromissione cognitiva, in presenza di un fenotipo clinico tipico (disturbo della memoria episodica con andamento progressivo in almeno 6 mesi e sindrome amnestica ippocampale, con deficit di rievocazione non corretto dal cueing,) e della presenza di almeno un biomarker (atrofia temporo-mesiale, livelli di Aβ o tau liquorali alterati, positività alla PET per amiloide o PET-FDG). Da questo approccio sono scaturite due importanti conseguenze: 1) l'esclusione del concetto di AD possibile, incompatibile con i nuovi criteri altamente specifici per AD, e 2) l'estensione della diagnosi allo stato prodromico, definito come MCI amnesico con evidenza neurobiologica di malattia. Il punto di forza di questi criteri è sembrato risiedere nella loro applicabilità a tutti gli stadi di malattia lungo il suo *continuum*. Sono tuttavia successivamente emersi i limiti di questa visione, quali il non aver preso in considerazione le forme atipiche o miste di AD e l'aver attribuito lo stesso peso a tutti i biomarker. Negli anni successivi, sono stati quindi compiuti importanti avanzamenti, frutto dell' acquisizione di nuove conoscenze fisiopatologiche. L'osservazione di marker di patologia AD in assenza di sintomi clinici ha portato ad includere nella diagnosi anche stadi preclinici, quali lo "stato asintomatico a rischio di AD" (soggetti asintomatici con prime lesioni cerebrali patologiche) e l' "AD presintomatico" (soggetti asintomatici portatori di note mutazioni autosomiche dominanti associate allo sviluppo inesorabile di AD). I biomarker sono stati inoltre distinti in due categorie, ovvero quelli *fisiopatologici* (livelli di Aβ, t-tau e p-tau nel liquor, e captazione di PIB alla PET) e *topografici* (ipometabolismo nelle regioni temporo-parietali alla PET con FDG e atrofia temporo-mesiale alla RM strutturale). I biomarker fisiopatologici supportano la presenza della sottostante patologia AD (*core* di malattia), mentre quelli topografici possono essere d'aiuto nel caratterizzare il fenotipo clinico e nel quantificare e monitorare la progressione della malattia. Lo stesso linguaggio scientifico è stato successivamente rivisto dai medesimi autori nel 2010 (39), con l'introduzione di definizioni innovative *("a new lexicon")* per gli stadi preclinici e asintomatici della malattia. Sono nati così i paradigmi di "soggetto asintomatico a rischio" per i soggetti in cui sono presenti biomarcatori di patologia amiloidea, e "presintomatici" per quei soggetti portatori di mutazioni geniche note dell'AD.

Il 2011 ha poi segnato un'ulteriore tappa

dell'evoluzione della diagnosi di AD, con i criteri del National Institute of Aging (NIA) e l'Alzheimer Association (AA) (criteri NIA-AA) che hanno definito 3 diversi stadi preclinici, in base alla presenza nel paziente di alterazioni espressione dei meccanismi fisiopatologici in sequenza, ovvero la deposizione di amiloide, l'aumento dei livelli di proteina tau con la successiva neurodegerazione, e poi il graduale sviluppo di deficit cognitivi (40). Nel 2014, una nuova iniziativa dell'IWG, sostanziata da nuove e più convincenti acquisizioni, ha poi proposto come requisiti nell'ambito del sistema diagnostico la presenza di un quadro tipico di demenza da AD dal punto di vista clinico, e di un biomarcatore di tipo fisiopatologico compatibile con patologia AD-like (41). I due sistemi sono stati successivamente rivisti nel 2016, nell'ambito di un tentativo di consenso sulla diagnosi preclinica di malattia, basata sia sull'evidenza di patologia amiloidea *in vivo* che sulla positività di tau nei casi di elevato rischio di progressione verso un quadro clinico di demenza tipo AD (42).

Attuali controversie

Nel 2018, il NIA e l'AA hanno proposto un sistema diagnostico, essenzialmente destinato a scopi di ricerca, denominato ATN (amyloid, tau, neurodegeneration) (43). Questo sistema, da applicarsi sia nella fase asintomatica che in quella sintomatica della malattia, riflette la tendenza a spostare l'approccio diagnostico da un piano clinico-biologico ad uno meramente biologico, non prendendo in considerazione, cioè, il quadro cognitivo del paziente (integrità, MCI o demenza). In base a questa versione del sistema NIA-AA, tuttavia, la diagnosi rimane basata esclusivamente sulla presenza di biomarcatori, in base alla condizione ATN. In questo contesto, quindi, pur in assenza di deficit cognitivi, lo status A+T+ corrisponde alla diagnosi di "malattia" di Alzheimer, mentre i pazienti caratterizzati da una condizione A+T- vengono definiti come "portatori" di patologia tipo Alzheimer nell'ambito di un *continnum* di malattia. Questo tipo di approccio ha tuttavia generato un diffuso dibattito fra gli addetti ai lavori, e sono state avanzate giustificate riserve su una definizione puramente biologica dell'AD, la quale finirebbe così con il ricomprendere al suo interno aspetti clinici assai diversi, dal soggetto cognitivamente integro al paziente con demenza di grado severo. Una prima limitazione a questo approccio, ad esempio, emerge dalla ripetuta osservazione negli studi, che il riscontro di una positività per proteine amiloide e tau in soggetti cognitivamente integri non possiede valore predittivo assoluto nei confronti della comparsa di disturbi (44) Questi soggetti non sono infatti destinati ad un inevitabile declino cognitivo, a fronte di stime di rischio di demenza lungo l'arco della vita del 12-42% (45), ma potrebbero essere considerati come "a rischio di progressione", con un successivo andamento clinico sia complessivamente stabile per lungo tempo, sia tendenzialmente progressivo verso una forma prodromica e/o una demenza. Questi due pattern evolutivi andrebbero poi separati in base alla presenza di fattori preventivi o di compenso (ad esempio, tra li altri, la riserva cognitiva e i fattori genetici), che possono modulare il livello di rischio agendo di concerto con le alterazioni neuropatologiche. Un'altra argomentazione che si può addurre contro un sistema diagnostico centrato sulle pure evidenze biologiche è quella per cui definire un paziente come affetto da AD solo sulla base dei biomarcatori può creare confusione nei casi di comorbidità. La positività per amiloide e tau non esprime infatti con sufficiente certezza la presenza di una patologia tipo AD, potendosi riscontrare anche in altre malattie neurodegenerative, ad esempio spesso nella malattia a corpi diffusi di Lewy (46), per non parlare dei soggetti cognitivamente integri di età più avanzata (47). Esistono poi quadri di patologia più rari, come la argyrophilic grain disease (AGD), la taupatia non-AD, e la limbic-predominant TDP-43 related encephalopathy (LATE), che presentano tutte fenotipi clinici simil-AD ma per i quali non sono al momento disponibili biomarcatori di malattia. Infine, un ulteriore elemento a sfavore di un approccio diagnostico esclusivamente biologico è che esso è inadeguato e fuorviante nel caso di soggetti di età molto avanzata, nei quali di fatto la presenza di disturbi cognitivi e patologie età-correlate rappresenta quasi la regola.

Un possibile avanzamento del sistema diagnostico potrebbe tener conto anche di altre considerazioni. Nei soggetti asintomatici, ad esempio, potrebbero essere proposti livelli diversi di rischio sulla base del loro profilo di biomarcatori, sia fisiopatologici (PET per amiloide, livelli liquorali di beta-amiloide), sia topo-

grafici (atrofia ippocampale alla RM, ipometabolismo alla FDG-PET). Il livello di rischio potrebbe poi essere ulteriormente affinato sulla base di informazioni relative all'età, alla comorbidità, allo status ApoE, e ad altri fattori. Numerose altre osservazioni, inerenti i valori di cut-off dei biomarcatori liquorali, lo scarso valore predittivo dei dati biologici – anche in relazione agli elevati costi - nei confronti dell'evoluzione clinica, e alcune riserve di carattere etico, suggeriscono come la diagnosi basata unicamente sui dati biologici in un soggetto asintomatico (ma anche, secondo le più recenti revisioni Cochrane, in un paziente con MCI) possa essere utilizzata in casi specifici per scopi di ricerca, ma non possa essere considerata attendibile nel *setting* clinico.

Altro tema attualmente dibattuto è il cosiddetto valore diagnostico incrementale (*incremental dignostic value*, IDV) dei marcatori biologici, ovvero il loro impatto sul processo diagnostico e l'ordine nel quale essi dovrebbero essere ricercati nell'ambito del workup clinico, onde ovviare all'esecuzione di accertamenti inutili e allo spreco di risorse. Al proposito, ad esempio, è stato osservato che in pazienti con diagnosi di AD effettuata in assenza di biomarcatori, la negatività della PET amiloide è in grado di modificare la diagnosi più frequentemente della negatività del pattern liquorale; la PET sembra dunque essere indicata prioritariamente rispetto all'indagine liquorale, consentendo una confidenza diagnostica maggiore (48).

Grande interesse riscuote anche, nella pratica clinica, la frequente coesitenza, in pazienti con deterioramento cognitivo, di aspetti che rimandano sia alla patologia vascolare che a quella di natura degenerativa amiloide. Per queste forme viene tuttora ampiamente utilizzato il termine di "demenza mista". I criteri diagnostici applicabili *in vivo* verosimilmente sottostimano la frequenza di questa categoria, in quanto studi anatomopatologici *post-mortem* rilevano come tra i soggetti più anziani vi sia una predominanza di demenza di tipo misto precedentemente diagnosticata in altro modo. Infatti, segni di microangiopatia cerebrale ed infarti sono di frequente riscontro anche in pazienti con diagnosi di sola AD, così come, per converso, l'atrofia dell'ippocampo ed aggregati di proteina-tau iperfosforilati sono riscontrabili in pazienti affetti da demenza vascolare. Vi sono molti criteri diagnostici utilizzabili per definire una demenza mista, ma nessuno opportunamente validato con studi neuropatologici. Ad oggi, per poter porre diagnosi, l'International Classification of Diseases (ICD-10) definisce come pazienti con demenza mista quei soggetti che soddisfano i criteri sia per AD che per demenza vascolare. Invece, l'International Working Group (IWG), dà una definizione basata sulla compresenza di evidenze cliniche e biologiche di entrambe le forme di demenza; per esempio, basse concentrazioni di β-amiloide ed elevate di proteina-tau nel liquido cerebrospinale associate al riscontro all'imaging di segni di patologia dei grossi o piccoli vasi; in questi casi, tuttavia, l'aspetto degenerativo deve essere considerato preminente, e la forma clinica meglio definita come "Alzheimer misto" ("*mixed Alzheimer")* (41). Il sempre più frequente riconoscimento della patologia nota come angiopatia amiloide cerebrale (CAA), caratterizzata da tipiche lesioni vascolari cerebrali diffuse e da assai frequente demenza clinica con caratteristiche Alzheimer-like (49), rende poi questo capitolo ancora più complesso e suscettibile di revisioni sulla base di nuove evidenze. Nel campo della demenza mista, l'utilizzo delle tecniche di RM convenzionale porta spesso a diagnosi controverse, per cui sono state sviluppate metodiche in grado di incrementare l'accuratezza diagnostica. Ad esempio, applicando protocolli ottimizzati di RM ad alta risoluzione, senza eccessivo consumo di tempo e risorse, è stato possibile osservare come le lesioni vascolari profonde della sostanza bianca e grigia sono più comuni nella demenza vascolare, mentre le lesioni microemorragiche *(microbleeds*) cerebrali, profonde e iuxtacorticali, predominano nella forma mista, il che suggerisce che la principale patologia sottostante sia la CAA (50). Altri studi hanno evidenziato come la RM con tensore di diffusione (DTI) con approccio *voxelwise* possa identificare specifiche alterazioni della sostanza bianca cerebrale (tratti paraippocampali, radiazione talamica) utili non solo nella diagnostica differenziale fra pazienti e soggetti normali, ma anche fra pazienti con demenza vascolare e pazienti con demenza degenerativa (51). Ulteriori metodiche in grado di incrementare l'accuratezza diagnostica, anche in senso predittivo in pazienti con forme iniziali, sono gli algoritmi di *machine learning* (ML) combinati con la RM. In questo modo, è possibile ottenere un utile supporto classificativo in quei pazienti nei quali la diagnosi (o la diagnosi prevalente) è incerta (52).

Conclusioni

In conclusione, gli avanzamenti degli ultimi anni, principalmente legati allo sviluppo di marcatori neurobiologici di malattia, ha significativamente modificato il processo diagnostico dell'AD. In attesa di nuove evidenze, l' approccio clinico-biologico (presenza di fenotipo clinico + evidenza biologica di patologia amiloide) sembra comunque essere, al momento, quello che può guidare il clinico ad una diagnosi più accurata di malattia, ma anche ad una migliore definizione dei casi in cui l'AD rappresenta una condizione comorbida.

Bibliografia

1. Welsh KA, Butters N, Hughes J, Mohs RC, Heyman A. Detection of anormal memory decline in mild cases of Alzheimer's disease using CERAD neuropsychological measures. Arch Neurol 1991; 48:278-281.
2. Deardorff WJ, Grossberg GT. Behavioral and psychological symptoms in Alzheimer's dementia and vascular dementia. Handb Clin Neurol. 2019;165:5-32.
3. Galton CJ, Patterson K, Xuereb JH, et al. Atypical and typical presentations of Alzheimer's disease: a clinical, neuropsychological, neuroimaging and pathological study of 13 cases. Brain 2000; 123:484-498.
4. Crutch SJ, Lehmann M, Schott JM, et al. Posterior cortical atrophy. Lancet Neurol 2012; 8: 451-464.
5. Henry ML, Gorno-Tempini ML The logopenic variant of primary progressive aphasia. Curr Opin Neurol 2010; 23:633-637.
6. Mendez MF, Joshi A, Tassniyom K, Teng E, Shapira JS. Clin ico-pathologic differences among patients with behavioral variant frontotemporal dementia. Neurology 2013; 80: 561-568.
7. Johnson JK, Head E, Kim R, Starr A, Cotman CW. Clinical and pathological evidence for a frontal variant of Alzheimer disease. Arch Neurol 1999; 56:1233-1239.
8. Alladi S, Xuereb J, Bak T, et al. Focal cortical presentations of Alzheimer's disease. Brain 2007;130:2636-2645.
9. Tsolaki M, Kokarida K, Iakovidou V, et al. Extrapyramidal symptoms and signs in Alzheimer's disease: prevalence and correlation with the first symptom. Am J Alzheimers Dis Other Demen. 2001; 16(5):268-278.
10. Haan MN, Jagust WJ, Galasko D, et al. Effect of extrapyramidal signs and Lewy bodies on survival in patients with Alzheimer disease. Arch Neurol 2002; 59:588-593
11. Ashton NJ, Leuzy A, Karikari TK, et al. The validation status of blood biomarkers of amyloid and phospho-tau assessed with the 5-phase development framework for AD biomarkers. Eur J Nucl Med Mol Imaging 2021; Mar 6. doi: 10.1007/s00259-021-05253-y.
12. Snider BJ, Fagan AM, Roe C, et al. Cerebrospinal fluid biomarkers and rate of cognitive decline in very mild dementia of the Alzheimer type. Arch Neurol 2009; 66: 638–645.
13. Fagan AM, Roe CM, Xiong C, et al. Cerebrospinal fluid tau/b-amyloid(42) ratio as a prediction of cognitive decline in nondemented older adults. Arch Neurol 2007;64: 343–349.
14. Fagan AM, Mintun MA, Shah AR, et al. Cerebrospinal fluid tau and ptau181 increase with cortical amyloid deposition in cognitively normal individuals: Implications for future clinical trials of Alzheimer's disease. EMBO Mol Med 2009;1: 371–380.
15. Zetterberg H, Andreasson U, Hansson O, et al. Elevated cerebrospinal fluid BACE1 activity in incipient Alzheimer disease. Arch Neurol 2008;65: 1102–1107.
16. Fukumoto H, Tokuda T, Kasai T, et al. High-molecular-weight beta-amyloid oligomers are elevated in cerebrospinal fluid of Alzheimer patients. FASEB J 2010;24: 2716–2726.
17. Hansson O, Zetterberg H, Buchhave P, et al. Prediction of Alzheimer's disease using the CSF Ab42/Ab40 ratio in patients with mild cognitive impairment. Dement Geriatr Cogn Disord 2007;23: 316–320.
18. Schoonenboom NS, Mulder C, Van Kamp GJ, et al. Amyloid 38, 40, and 42 species in cerebrospinal fluid: More of the same? Ann Neurol 2005;58: 139–142.
19. Jack CR, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 2010; 9(1): 119-128.
20. Braak H, Braak E. Demonstration of amyloid deposits and neurofibrillary changes in whole brain sections. Brain Pathol. 1991; 1(3):213-216.
21. Chiotis K, Saint-Aubert L, Savitcheva I, et al. Imaging in-vivo tau pathology in Alzheimer's disease with THK5317 PET in a multimodal paradigm. Eur J Nucl Med Mol Imaging. 2016; 43(9): 1686–1699.
22. Rocher AB, Chapon F, Blaizot X, et al. Resting-state brain glucose utilization as measured by PET is directly related to regional synaptophysin levels: a study in baboons. NeuroImage 2003;20(3):1894-1898.
23. Johnson KA, Fox NC, Sperling RA, et al. Brain imaging in Alzheimer disease. Cold Spring Harb Perspect Med. 2012;2(4):a006213. doi: 10.1101/cshperspect.a006213.
24. Raichle ME, MacLeod AM, Snyder AZ, et al. A default mode of brain function. Proc Natl Acad Sci 2001;98: 676–682.
25. Lehmann M, Ghosh PM, Madison C, et al. Diverging patterns of amyloid deposition and hypometabolism in clinical variants of probable Alzheimer's disease. Brain. 2013 Mar;136(3):844-558.
26. Woodward MC, Rowe CC, Jones G, et al. Differentiating the frontal presentation of Alzheimer's disease with FDG-PET. J Alzheimers Dis. 2015; 44(1):233-242.
27. Gosche KM, Mortimer JA, Smith CD, et al. Hippocampal volume as an index of Alzheimer neuropathology: findings

from the Nun Study. Neurology 2004;58: 1476–1482.
28. Killiany RJ, Hyman BT, Gomez-Isla T, et al. MRI measures of entorhinal cortex vs hippocampus in preclinical AD. Neurology 2002;58: 1188–1196.
29. Chan D, Janssen JC,Whitwell JL, et al. Change in rates of cerebral atrophy over time in early-onset Alzheimer's disease: Longitudinal MRI study. Lancet 2003;362: 1121–1122.
30. DeCarli C, Frisoni GB, Clark CM, et al. Qualitative estimates of medial temporal atrophy as a predictor of progression from mild cognitive impairment to dementia. Arch Neurol 2007; 64: 108–115.
31. Cotta Ramusino M, Altomare D, Bacchin R, et al., Medial temporal lobe atrophy and posterior atrophy scales normative values. Neuroimage Clin. 2019; 24:101936. doi: 10.1016/j.nicl.2019.101936.
32. Chan D, Fox NC, Jenkins R, et al. Rates of global and regional cerebral atrophy in AD and frontotemporal dementia. Neurology. 2001;57(10):1756-1763.
33. Jack CR, Holtzman DM. Biomarker modeling of Alzheimer's disease. Neuron 2013;80(6):1347-1358.
34. Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories.
Neurobiol Aging. 1997; 18:351–357.
35. Jack CR, Wiste HJ, Weigand SD, et al. Amyloid-first and neurodegeneration-first profiles characterize incident amyloid PET positivity. Neurology. 2013;81(20):1732-1740.
36. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984;34(7):939-944.
37. Varma AR, Snowden JS, Lloyd JJ, et al. Evaluation of the NINCDS-ADRDA criteria in the differentiation of Alzheimer's disease and frontotemporal dementia. J Neurol Neurosurg Psychiatry. 1999; 66(2):184-188.
38. Dubois B, Feldman HH, Jacova C, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol. 2007;6(8):734-746.
39. Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol 2010; 9: 1118–1127.
40. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7: 280–292.
41. Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol. 2014; 13(6):614-629.
42. Jack CR, Bennett DA, Blennow K, et al. A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers. Neurology. 2016; 87: 539–547.
43. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's Dement 2018; 14: 535–562.
44. Yu JT, Li JQ, Suckling J, et al. Frequency and longitudinal clinical outcomes of Alzheimer's AT(N) biomarker profiles: A longitudinal study. Alzheimer's Dement 2019; 15: 1208–1217.
45. Brookmeyer R, Abdalla N. Estimation of lifetime risks of Alzheimer's disease dementia using biomarkers for preclinical disease. Alzheimer's Dement 2018; 14: 981–988.
46. Robinson JL, Lee EB, Xie SX, et al. Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated. Brain 2018; 141: 2181–2193.
47. Boyle PA, Yang J, Yu L, et al. Varied effects of age-related neuropathologies on the trajectory of late life cognitive decline. Brain 2017; 140: 804–812.
48. Ramusino MC, Garibotto V, Bacchin R, et al, Incremental value of amyloid-PET versus CSF in the diagnosis of Alzheimer's disease. Eur J Nucl Med Mol Imaging 2020; 47(2):270-280. doi: 10.1007/s00259-019-04466-6, pp. 1-11.
49. Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, et al, Cerebral amyloid angiopathy and Alzheimer disease — one peptide, two pathways. Nat Rev Neurol 2020; 16, 30–42.
50. Cotta Ramusino M., Vitali P., Anzalone N., et al, Vascular lesions and brain atrophy in Alzheimer's, vascular and mixed dementia: an optimized 3T MRI protocol reveals distinctive radiological profiles. Curr. Alzheimer Res. 2022 Jun 20. doi: 10 .2174/1567205019666220620112831 (online ahead of print).
51. F. Palesi, A. De Rinaldis, P. Vitali, et al, Specific patterns of white matter alterations help distinguishing Alzheimer's and Vascular Dementia. Front. Neurosci. 2018; 12 (274):1-14.
52. G. Castellazzi, M. G. Cuzzoni, M. Cotta Ramusino, et al, A machine learning approach for the differential diagnosis of Alzheimer and vascular dementia fed by MRI selected features. Front. Neuroinformatics 2020; 14:25. doi: 10.3389/fninf.2020.00025

Correspondence:
Alfredo Costa
Dipartimento di Scienze del Sistema Nervoso e del Comportamento, Università di Pavia
E-mail: alfredo.costa@mondino.it

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The Italian contribution to the anatomo-clinical method and physical examination in the history of neurology

Francesco Brigo[1], *Mariano Martini*[2], *Lorenzo Lorusso*[3]

[1]Department of Neurology, Hospital of Merano (SABES-ASDAA), Italy; [2]Department of Health Sciences, University of Genoa, Italy; [3]UOC Neurology and Stroke Unist, ASST Lecco, Merate, Italy

Abstract. In Italy, neurology was constituted as a distinct and autonomous field only at the end of the 19th century. The recent neurological advances made in France were rapidly introduced and widely discussed among the Italian scientific community. The anatomo-clinical method applied by Jean-Martin Charcot (1825–1893) and his pupils to neurological disorders was immediately accepted and further refined by the Italian physicians. This led to important contributions to the physical examination with the description of new signs and tests for the diagnosis of various neurological disorders.

Keywords: Italy, neurology, history of Neurology

Il contributo italiano al metodo anatomo-clinico e all'esame obiettivo nella storia della Neurologia

Riassunto. In Italia la neurologia clinica si costituì come una branca autonoma e distinta solamente alla fine del XIX secolo. Le recenti scoperte e gli avanzameni in ambito neurologico realizzati in Francia furono introdotti rapidamente e ampiamente discussi nella comunità medico-scientifica italiana. Il metodo anatomo-clinico applicato da Jean-Martin Charcot (1825–1893) e dai suoi allievi alla Neurologia fu prontamente accettato e ulteriormente adattato e rifinito dai medici italiani, portando a rilevanti contibuti alla semeiologia neurologica, con la descrizione di nuovi segni tuttora utili per la diagnosi di malattie neurologiche.

Parole chiave: Italia, Neurologia, Storia della neurologia

Introduction

At the end of the 19th Century, Paris was the center of the neurological world, and Jean-Martin Charcot (1825-1893) was the leading figure in the field of neurology (1,2). The French master had developed and applied the anatomo-clinical method to the study of neurological disorders, an achievement that can be regarded as his greatest and most enduring legacy (3). Nowadays, neurologists continue to use this method: based on a detailed clinical history and physical examination, in most cases they can identify with utmost precision the location of the lesion(s) responsible for patients' symptoms.

In this article we provide a succinct overview of the Italian contribution to the anatomo-clinical method and physical examination in neurology, emphasizing the initial influence of Charcot and his pupils, and the original role played by several Italian physicians in the description of new signs and tests for the diagnosis of various neurological disorders.

Learning from the Master: Italian physicians and Jean-Martin Charcot (1825-1893)

Several Italian physicians at the turn of the 19th Century moved to Paris to study under Charcot and

his pupils, attending the famous lessons given by the French neurologist at La Salpêtrière Hospital in Paris (4). During their stay they took notes and once they came back to Italy translated these memories into Italian and published them. In doing so, they greatly contributed to the early dissemination of the most recent development in the field of clinical neurology across Italy. Furthermore, these translations provide information that cannot be found elsewhere in Charcot's corpus of works, and therefore are an invaluable and unique source to fully understand some of the ideas and theories proposed by Charcot (4).

In 1884, the famous Italian physician Gaetano Rummo (1853–1917) published the Italian translation of all lectures on aphasia delivered by Charcot in the summer of 1883, which represents the only complete collection of these lessons, and includes the first reproduction of the "Charcot's bell" diagram, showing the centers involved in language production (5). Charcot himself wrote the preface to the volume, praising the efforts made by Rummo in his work of translation and dissemination. In 1890, Rummo published a book with a series of 70 photos depicting the "Great Hysteria" or "hystero-epilepsy", paying an explicit homage to the four sequential phases of hystero-epilepsy described by Paul Richer (1849–1933) and Charcot (6). Just like his master, Rummo practiced hypnotic therapy in Naples and was a pioneer in the use of video and phonograph to document animals and patients with various neurological disorders.

A further Italian physician, Domenico Miliotti (1851-1888), attended all the "Friday lectures" given by Charcot in the academic year 1883/1884, translated them into Italian, and published them in 1885 (7). He greatly praised the practice-oriented teachings by Charcot (that he called *"lezioni di cose"*, lessons by (or about) things). Some of the topics discussed at length and in detail in these lessons include hysterical sleep *("attacco di sonno"*, sleep attack), "music aphasia" and "music agraphia" without verbal aphasia, Friedreich's ataxia, and prolonged hysterical fits *("stato di male istero-epilettico"*, hystero-epileptic status).

Giulio Melotti (1857–?) also studied at la Salpêtrière under Charcot from 1884 to 1886, making some transcriptions of his lectures that cannot be found elsewhere (8,9). They include lectures on intermittent claudication, convulsive tics with coprolalia and echolalia, and other selected topics.

The fascination exerted on Italian physicians by Charcot and his school persisted also beyond his death and continued to attract people eager to acquire extensive clinical learning on neurological disorders. Among them, one should mention the fascinating figure of Vincenzo Neri (1880-1960), who became a close friend of Charcot's pupil Joseph Jules François Félix Babiński (1857-1931), and a pioneer in the use of the cinematograph in neurology (10).

The Italian contribution to the physical examination in neurology

As surprising as it might be, neither Charcot nor his pupil Babiński ever published a systematic textbook on the anatomo-clinical method and the physical examination in neurology. The earliest book entirely devoted to these issues was published in 1889 by Leonardo Bianchi (1848–1927) to provide a practice-oriented description of neurological semiology for physicians and medical students (11). It describes the full spectrum of neurological examination in detail starting from neurological signs and presenting them according to the underlying neuroanatomical lesions. With its eight chapters, each devoted to a specific symptom/sign, this book provides a detailed description of each symptom/sign, enriched by useful tips to improve clinical examination, and a concise overview of underlying anatomical substrates (12).

As this example clearly shows, neurological advances made in France were rapidly introduced and widely discussed in the Italian scientific community. Italians were ready to rapidly accept and refine the anatomo-clinical method applied by Charcot and his successors, recognizing its clinical usefulness in identifying and diagnosing various neurological disorders. Furthermore, they described new signs and were able to provide detailed and accurate explanations of their underlying mechanisms.

Of note, major contributions of Italian physicians to the neurological examination were devoted to clinical disorders arising as a consequence of a pyramidal tract dysfunction. The pyramidal tract, first

described in detail by Ludwig Türck in 1852 (13), is a motor pathway including fibers that carry signals from the motor areas of the cortex, where the cell bodies of the upper (or first) motoneurons are located, to the brainstem or spinal cord, where axons of these cells eventually make synaptic connection with the lower (or second) motoneurons.

In 1896, Babiński had very succinctly described a sign to detect a pyramidal tract dysfunction (14). This sign, widely known as the Babinski sign or extensor toe sign, is elicited by stroking along the lateral border of the foot sole: this stimulation leads to an upward movement of the big toe (dorsal flexion). This phenomenon is commonly found in newborns and infants, and subsequently disappears as a consequence of inhibition from upper neuronal centers (15). After one year of age, the normal response to stimulation of the foot sole is a downward movement (flexion) of the big toe. Conversely, a dorsal flexion of the big toes (Babinski sign) is invariably a sign of pyramidal tract dysfunction (Figure 1).

Just three years after its first description, between the 26th and 28th of June 1899, a series of meetings were held in Naples, where some Italian physicians discussed at length the clinical value of the Babinski sign.

Giovanni Boeri (1867–1946) reported having found this sign in 76% of patients with acute or chronic hemiplegia (16). It was absent in some patients with muscular atrophy and amyotrophic lateral sclerosis but was invariably found in Erb-Charcot paralysis (spastic paraplegia due to syphilitic meningomyelitis). Furthermore, in cases of traumatic myelitis affecting the upper segments of the spinal cord, it could be absent. Based on our current knowledge, we now know that the Babinski sign can lack in patients with a spinal shock due to the temporary inexcitability of spinal motor neurons. Furthermore, as Boeri himself pointed out, the Babinski sign can be elicited only if the peripheral nerves and muscles mediating the reflex are intact (16). Hence, immediately after its description, it was recognized that this sign has a suboptimal sensitivity to detect a pyramidal tract dysfunction, and it needs to be interpreted considering the whole clinical picture (17).

Concerning its specificity, during a lecture given on 1st July 1899 at a meeting of the Lancisian Society of the Hospitals of Rome, Vincenzo Giudiceandrea (dates unknown) claimed that the Babinski sign could be observed «in cases where one cannot suspect a lesion of the pyramidal pathways (hysteria); conversely, in some cases, where such a lesion certainly exists, the normal movement of flexion can occur» (18). Nowadays, we know that the Babinski sign has a very high specificity for pyramidal tract dysfunction. The incorrect criticisms raised by Giudiceandrea were probably due to very few details on how to evoke correctly the sign in clinical practice (the first description provided by Babiński in 1896 was extremely succinct and could leave room for uncertainty).

During the same meeting in Rome, the famous Italian physician Giovanni Mingazzini (1859–1929) provided what remains the most appropriate interpretation of the mechanisms underlying the Babinski sign (18).

As he noted, «The movement of toes following the stimulation of the foot sole could be regarded as part of a set of automatic movements involving upward flexion of the foot and flexion of the leg and thigh, rather than as a real reflex». Mingazzini mentioned the flexor synergy of the lower limb following plantar stimulation that had been first described by Édouard Brissaud (1852–1909) in 1896 (19). As Mingazzini correctly understood, the Babinski sign is a complex series of motor phenomena that are found in newborns and infants, but are later masked by inhibition from upper neuronal centers. However, this central motor pattern remains rooted in the central nervous system and can reemerge after a pyramidal system dysfunction (20).

In the following years, other physicians provided alternative methods or described new signs to detect a pyramidal tract dysfunction.

In 1912, Camillo Negro (1861-1927), an important Italian neurologist at the turn of the 19th Century and a pioneer in the use of video recordings in neurology (21,22), observed that when the patient lying in dorsal decubitus position raises the paretic limb with the leg extended on the thigh, there occurs an upward movement of the big toe, which is entirely consistent with the Babinski sign (23). This method clearly shows that the Babinski sign cannot simply be regarded as an

exteroceptive reflex following the stimulation of a bodily surface, but it can be evoked also by the activation of proprioceptive pathways involving muscle contractions or tendon stretching (24). Furthermore, Negro described how cold could facilitate the appearance of the Babinski sign and proposed the use of (faradic) electrical stimulation to evoke it (24).

In 1913, in an article published in Revue Neurologique, Giovanni Mingazzini described two "*petits signes*" ("small signs") or "*indices de luxe*" ("luxury clues") to detect slight organic paresis (25). The first sign was the arm test, which he called *"signe du serment"* ("oath sign"). Nowadays, although the name of Mingazzini is widely forgotten, this sign continues to be used to detect a paresis due to a stroke (it is part of the so-called Face Arm Speech Test, FAST) and to objectively quantify the functional impairment following a stroke (it is part of the National Institutes of Health Stroke Scale or NIHSS). The second sign described by Mingazzini was the "orbiculo-palpebral sign" (*"le signe de l'orbiculaire des paupières"*), which was proposed to detect the mild muscle impairment of the upper half of the face occurring in central facial palsy.

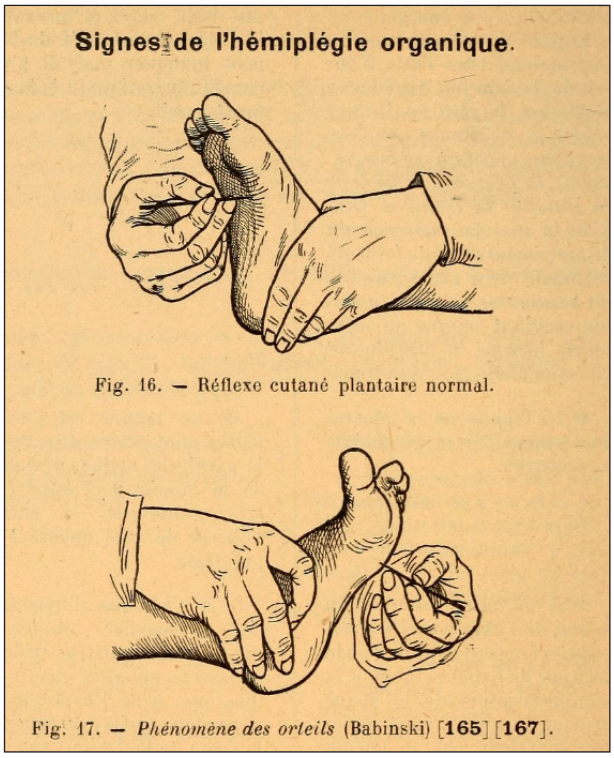

Figure 1: Drawings illustrating the normal toe phenomenon (upper figure) and the Babinski sign (lower figure).
From: Babinski J, Froment J. Hystérie-pithiatisme et troubles nerveux d'ordre réflexe en neurologie de guerre.
Paris: Masson et Cie; 1917 pag. 178

A further sign to identify pyramidal tract dysfunction was described by Vincenzo Neri in 1909 (26). He observed that «in a patient standing with the legs apart and the arms crossed on the chest if one makes him bend his trunk on his pelvis, telling, him to hold straight his legs, one observes that at a certain moment (when the trunk has almost reached the horizontal line) the leg on the paralyzed side flexes on a certain degree, whereas the unaffected leg remains extended». According to Dimitrie Noica (1869-1937), this sign reflects spinal hyperfunction emerging after a pyramidal lesion (27). Hence, it should be interpreted as a part of a triple flexion reflex (*"mouvement de defense"*, "defensive movement"), the shortening of the extremity, with flexion at the hip and knee and dorsiflexion at the ankle, that occurs after stimulation of the lower limb in patients with pyramidal tract lesions (10). After the acute lesion, the sign described by Neri could reflect an unusual pattern of flexor spasticity of the lower extremity, which was described in detail only in 1935 (28).

Conclusions

In Italy, neurology emerged as a distinct and autonomous field at the end of the 19th century (29,30). Neurological advances made in France were rapidly introduced and widely discussed among the Italian scientific community, which accepted and refined the anatomo-clinical method applied by Jean-Martin Charcot and his pupils. Many Italian physicians provided relevant contributions in the refinement of the physical examination and in the description of new signs and tests that retain their clinical value for the diagnosis of various neurological disorders.

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References

1. Brigo F, Balasse A, Nardone R, Walusinski O. Jean-Martin Charcot´s medical instruments: Electrotherapeutic devices in La Leçon Clinique à la Salpêtrière. J Hist Neurosci. 2021 Jan-Mar;30(1):94-101
2. Brigo F. Jean-Martin Charcot (1825-1893) and his second thoughts about hysteria. Arq Neuropsiquiatr. 2021 Feb;79(2):173-174.
3. Brigo F, Zanchin G, Martini M, Lorusso L; Study Group on the History of Neurology of the Italian Neurological Society. Jean-Martin Charcot (1825-1893) and the "Alice in Wonderland syndrome". Neurol Sci. 2022 Mar;43(3):2141-2144.
4. Brigo F, Lattanzi S, Martini M, Bragazzi N, Nardone R, Walusinski O. "Spreading the word of the master": the contribution of Italian physicians in the early dissemination of Jean-Martin Charcot's theories. Neurol Sci. 2020 Dec;41(12):3787-3794.
5. Charcot JM (1884) Differenti forme d'afasia. Lezioni fatte nella Salpêtrière nel semestre d'estate dell'anno 1883, redatte col consenso dell'autore dal dottore G. Rummo. Vallardi, Milano.
6. Rummo G (1890) Iconografia fotografica del Grande Isterismo—Istero-Epilessia pubblicata dal Prof. Gaetano Rummo. Omaggio al Prof. Camillo Bozzolo. Tipografia Angelo Trani, Napoli
7. Charcot JM (1885) Lezioni cliniche dell'anno scolastico 1883–84 sulle malattie del sistema nervoso. Redatte dal Dottor Domenico Miliotti. Vallardi, Milano
8. Charcot JM (1884) Della claudicazione intermittente, &c./ Lez. raccolte dal Dr. G. Melotti di Bologna. Gaz. degli Ospitali, No. 73
9. Charcot JM (1885) Intorno ad alcuni casi di tic convulsivo con coprolalia ed ecolalia: Analogia col jumping di Beard, il latah della Malesia ed il miriachit di Hammond, lezione raccolta G. Melotti. La Riforma Medica, 1885;1:184; 2:185; 2:186: 2
10. Brigo F, Benna P, Venturini S, Martini M, Lorusso L; Study Group on the History of Neurology of the Italian Neurological Society. Vincenzo Neri (1880-1960) and his sign to detect leg weakness due to corticospinal tract injury. Neurol Sci. 2022 May 7. doi: 10.1007/s10072-022-06115-7.
11. Bianchi L (1889) Appendice di Semeiotica delle Malattie del Sistema Nervoso. Francesco Vallardi, Milano.
12. Brigo F. Leonardo Bianchi (1848-1927) and the earliest book dedicated to neurological examination. Neurol Sci. 2022 May;43(5):3459-3461.
13. Türck L (1852) Über secundäre Erkrankung einzelner Rückenmarkstränge und ihrer Fortsetzung zum Gehirne. Akad Wissensch Wien Math Naturwiss Class Sitzungber.
14. Babinski J (1896) Sur le réflexe cutané plantaire dans certaines affections organiques du systeme nerveux central. Compt Rend Soc Biol 48:207–208
15. Brigo F, Caglioti F. Babinski sign in the only existing sculpture by Leonardo. Childs Nerv Syst. 2021 Apr;37(4):1029-1031.
16. Boeri G (1899) Sul fenomeno di Babinski. Riforma medica. Anno XV:146-148.
17. Brigo F, Lattanzi S, Nardone R. The Babinski sign in the first Italian reports. Neurol Sci. 2021 Jun;42(6):2595-2598.
18. Giudiceandrea V (1899) Sul cosidetto fenomeno delle dita del piede di Babinski. Bullettino Soc. Lancisiana degli Ospedali di Roma. Anno XIX; 1:226–227.
19. Brissaud E (1896) Le réflexe du fascia lata. Gazette hebdomadaire de Médecine et de Chirurgie 43:253–256.
20. Brigo F, Lorusso L; Study Group on the History of Neurology of the Italian Neurological Society. Adolph Seeligmüller (1837-1912) and the first graphic illustration of the "toe phenomenon" (later called "Babiński sign") in the medical literature. Neurol Sci. 2022 Mar;43(3):2145-2148.
21. Brigo F, Lorusso L; Study Group on the History of Neurology of the Italian Neurological Society. Camillo Negro (1861-1927) and the "bulbo-palpebral hyperkinetic phenomenon" in peripheral facial palsy. Neurol Sci. 2022 Mar;43(3):2149-2152.
22. Brigo F, Di Gennaro G, Morano A, Sironi VA, Lorusso L; Study Group on the History of Neurology and of the Study Group on Epilepsy of the Italian Neurological Society. Camillo Negro (1861-1927) and Antonio Carle (1854-1927): Pioneers of non-resective surgical approach to epilepsy treatment. Epilepsy Behav. 2021 Dec;125:108360.
23. Negro C (1912) Patologia e clinica del sistema nervoso: lezioni del Prof. Camillo Negro. Lattes, Torino.
24. Brigo F, Norata D, Benna P, Lorusso L; Study Group on the History of Neurology of the Italian Neurological Society. Camillo Negro (1861-1927) and his method for eliciting the extensor toe sign. Neurol Sci. 2022 Apr; 43(4):2887-2889.
25. Mingazzini G (1913) Sur quelques "petits signes" des paresies organiques. Rev neurol 20:469–473.
26. Neri V (1910) Sur un nouveau signe d'hémiplegie organique. Nouvelle Iconographie de la Salpétrière. pp 88–89.
27. Noica DDM, Paulian MM, Sulica A (1912) Le mécanisme du signe de Kernig et du signe du member inférieur de Néri. L'encéphale 7:118–126
28. Langworthy OR, Highberger E, Foster R (1935) Hemiplegia with the leg in flexion. Arch NeurPsych 34:520–532
29. Mazzarello P. Breve profilo delle scienze neurologiche in Italia dalla fine dell'Ottocento alla prima metà del Novecento, in "Medicina nei Secoli" vol. 30, pp. 75-104 (2018).
30. Bentivoglio M, Mazzarello P. History of neurology in Italy. In: History of Neurology. S. Finger, F. Boller, K.L. Tyler, Editors. Handbook of Clinical Neurology, Vol. 95 (3rd series), 2010 Elsevier.

Correspondence:
Mariano Martini
Department of Health Sciences, University of Genoa, Italy
E-mail: mariano.yy@gmail.com

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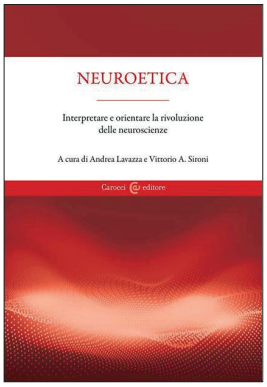
di Paolo Mazzarello
Edizione: Neri Pozza

Il protagonista, il colpevole di questo giallo efferato e cupo, è indicibile. Non puoi dargli un nome e non puoi svelarlo. Ma quando uno storico della scienza come Paolo Mazzarello decide di scrivere un romanzo, e un romanzo di delitti e di misteri, ha una sola strada possibile: mettere nel libro tutto quello che un lettore non si aspetterebbe, ovvero filosofia e logica. Ma non solo, l'autore racconta una storia di omicidi, compiuti da qualcuno, che sembrano obbedire a una logica, a un disegno, come nella migliore tradizione giallistica, che seguono un filo, unico appiglio per degli investigatori sgomenti e turbati. Peccato che questo filo sia governato dal caos, dall'imponderabile, da una mente superiore che si ha persino paura di scoprire, perché il fatto stesso che possa esistere cambia il nostro modo di guardare il mondo, e mette in profonda crisi la nostra idea positiva della scienza e della tecnologia. È una terra di nessuno quella in cui si muovono i personaggi di questo libro, che comincia con un delitto in un mulino negli Stati Uniti e con un rapimento, e continua a crescere come fosse una foresta, un bosco narrativo che non ha disegnato nessuno, dove non ci sono sentieri. Mazzarello ci porta in un mondo diverso da quello frequentato dai giallisti tradizionali. Non si tratta soltanto di commissari e di pazzi maniaci che mandano mail misteriose, non si tratta di capire cosa accade ma soprattutto perché accade. E in quel perché c'è una vera e propria teologia, c'è il male e il caso, l'orrore e l'indifferenza. Con grande abilità l'autore del Mulino di Leibniz ci conduce dove nessuno di noi saprebbe arrivare con le proprie forze. E conferma la vecchia ipotesi di Borges: l'unico giallo che si deve ancora scrivere è quello dove l'assassino è il lettore.



Neuroetica. Interpretare e orientare la rivoluzione delle neuroscienze

A cura di Andrea Lavazza e Vittorio A. Sironi
Edizione: Carocci

Le conoscenze sul funzionamento del cervello sono in rapida accelerazione. Le acquisizioni delle neuroscienze risultano fondamentali per la medicina, ma permettono anche di comprendere le basi dei nostri comportamenti e offrono la possibilità di modificarli. Siamo di fronte a una rivoluzione che ridefinisce i concetti di mente, identità, libertà e che si estende a molti ambiti dell'esistenza poiché influenza la morale, il diritto e l'economia. Le neurotecnologie aprono inoltre scenari di controllo diffuso e prospettano l'opportunità di potenziarci cognitivamente e moralmente, di modificare i ricordi, di creare cervelli in laboratorio. Tutto ciò ha bisogno di un'attenta analisi e di una valutazione etica che deve essere condotta in modo interdisciplinare. È il campo della neuroetica ed è quanto si prefigge il volume presentando i temi più discussi a livello internazionale. Una guida imprescindibile per studiosi, decisori pubblici e cittadini consapevoli.

In memoriam

In ricordo del prof. Marcello Imbriani (1951- 2022)

Carlo Caltagirone
Direttore Scientifico, Fondazione Santa Lucia IRCCS, Roma

Il 19 luglio 2022 ci ha lasciato all'età di 70 anni il Prof. Marcello Imbriani, Professore Ordinario di Medicina del Lavoro all'Università degli Studi di Pavia e fondatore della S.I.R.A.S. (Società Italiana Riabilitazione di Alta Specializzazione).

È stato uno dei più conosciuti ed apprezzati studiosi del settore, autore di oltre 350 pubblicazioni tra lavori sperimentali, libri e pubblicazioni ad uso didattico.

La sua attività di clinico e ricercatore si è svolta interamente presso l'Ateneo Pavese e presso gli Istituti Clinico Scientifici Maugeri, I.R.C.C.S. di cui è stato apprezzato Direttore Scientifico.

La sua attenzione di scienziato si è concentrata soprattutto sui fattori di rischio negli ambienti di vita e di lavoro, culminante con la messa a punto e la standardizzazione di metodiche strumentali e di laboratorio e la loro applicazione nella valutazione dei rischi occupazionali, soprattutto a carico dell'apparato respiratorio e nelle ricerche sugli adattamenti cardio-respiratori e metabolici all'esercizio muscolare nel soggetto normale, nell'atleta, in diverse situazioni patologiche.

Ha rivestito, tra gli altri, gli incarichi di Direttore del Dipartimento di Sanità Pubblica, Neuroscienze, Medicina Sperimentale e Forense; Direttore del Corso di Laurea in Terapia Occupazionale; Direttore del Centro di Ricerche in Fisiopatologia e Sicurezza del Lavoro; Presidente del Comitato di Bioetica degli Istituti Clinici Scientifici Maugeri; Direttore Sanitario del CNAO (Centro Nazionale Adroterapia Oncologica).

Quello che ci mancherà particolarmente sarà la sua solida preparazione, la sua lungimiranza nel cogliere gli aspetti di convergenza tra aree disciplinari e linee di ricerca, la sua naturale discrezione e riservatezza nel relazionarsi, la sua speciale gentilezza verso collaboratori e colleghi, la sua capacità di descrivere con ironia e modestia anche le più complesse imprese scientifiche, professionali ed umane.

A me mancherà un amico generoso, capace di coinvolgere con delicatezza e discrezione, curioso ed aperto anche agli sviluppi più innovativi delle discipline cliniche, sensibile e profondo in tutte le occasioni.

È stato un grande Presidente della S.I.R.A.S. e noi tutti ci auguriamo di poter proseguire, con il suo esempio sempre vivo, verso gli obiettivi che ha delineato.

(Fonte: Newsletter SIRAS www.sirasonline.it)

AIM OF THE JOURNAL

Confinia Cephalalgica et Neurologica publishes, with quarterly periodicity, theoretical and experimental contributions of biomedical researches and in human sciences of a multidisciplinary nature, primarily dedicated to Clinical Neuroscience, with particular but not exclusive, reference to the study, diagnosis and treatment of headaches and other headaches, in the broadest sense of syndromes and complex painful manifestations on the borders between nature and culture, between mind and brain, archetypes, behaviors and lifestyle. The new editorial plan of the magazine reflects, in its architecture, an idea of "forum circle", "gym constellation" of researches and contributions that, starting from the central core of headaches and related adaptive disorders, develops in increasingly broad circles of reflection and insights in the belief that the communication of science should not speak only English and that the journal can be a tool to constitute a network of connection between non-English speaking populations. It is no coincidence that the titles, abstracts and keywords of the contributions are also published in Spanish and/or Portuguese.

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The files, combined to a letter with the details in order to easily contact the Authors, must be sent to the Publisher to:
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at least 20 days before the publication of the issue (approximately mid-February; mid-June, mid-October).
All files must have the following requirements: - text: Word version for Windows; - tables: in Word or Excel format version for Windows; - charts: in Power Point format version for Windows.
The text must not exceed 10 typed folders (A4 format, double space, 30 lines per page, 60 characters), including the bibliography (max 25 bibliographic entries).
The first page must contain the title of the article, the full name and surname of the Authors, the Institutes to which they belong, the address of the first Author, the abstract of a maximum length of 10 lines and at least three Key Words.
Article in English language requires title, abstract and key word only in English. Article in Italian or Spanish/Portuguese, requires title, abstract and key words in the respective language and also in English.
The original articles should normally be divided into: introduction, material and methods or case report, results, discussion.

TABLES - Tables (in number not exceeding half of the pages of text) must have a concise title and be numbered with Arabic numerals. All abbreviations used must be clearly defined.
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REFERENCES - References must be reported in the text in brackets and in Arabic number [e.g. (1) or (1,2)]. The list of References must be reported at the end of the article and numbered consecutively in the order in which they are first mentioned in the text. In the references must be reported:
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- for journals (Vancouver style): Anthony M, Hinterberger H, Lance JW. Plasma serotonin in migraine and stress. Arch Neurol 1967; 16:544-552;
- for books: Kudrow L. Cluster headache: mechanism and management. New York: Oxford University Press 1980; 1-18.

Barzizza F, Cresci R, Lorenzi A. ECGraphic alterations in patients with cluster headache. In: Richichi I. & Nappi G. eds. Headaches of cardiovascular interest. Rome: Cluster Press 1989; 7:133-13;
- for abstract: 4) Caffarra P, Cammelli F, Scaglioni A et al. Emission tomography (SPELT) and dementia: a new approach. J Clin Exp Neuropsychol 1988; 3:313 (abstract).

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