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Aging, cognitive decline, and manual preference: Descriptive and correlational analyses

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Abstract

The aim of the study was to explore the prevalence of non-right handers, including "forced right-handers", in a sample of older people with cognitive impairment as well as the relationship with different levels of cognitive deterioration. The incidence of familial left-handedness was also explored.

The sample was composed of 246 subjects: 109 males and 137 females with a mean age of 73.24 years old, who were classified by the severity of cognitive decline (N = 115 mild, N = 75 moderate, N = 56 severe cognitive deterioration).

The results confirmed the prevalence of non-right handers in our sample and the relationship between manual preference and levels of cognitive decline. The non-right handers group was more than half of our sample and the forced right-handers were the majority in both mild, moderate, and severe levels of cognitive deterioration. The study of laterality, in addition to other well-known factors predictive of dementia, may be useful to prevent the vulnerability for neurodegenerative diseases at their earliest stages and to plan timely treatments.

Keywords: Manual preference; Aging; Cognitive decline; Mild Cognitive Impairment.

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1. Introduction

Getting old is a phase of life in which people experience significant changes in anatomical, psychological and social aspects. Physiological changes may explain the reduction of efficiency of different functions, including cognitive functions. Frequently, clinical symptoms of degenerative diseases appear in the elderly population. Neurodegenerative disease is common during the aging process, the consequences on social and health policies are often dramatic and require the selection of predictive factors useful to plan preventive interventions (Di Nuovo, De Beni, Borella, Marková, Laczó, & Vyhnálek, 2020).

Dementia describes a heterogeneous group of age-related disorders, characterized by the progressive neurodegeneration of the brain cells and resources (Tiepolt, Patt, Aghakhanyan, Meyer, Hesse, Barthel *et al.*, 2019). Age, gender, familiarity of dementia, low education, vascular disorders (hypertension, dyslipidemia, diabetes) and alcohol intake seem to promote an acceleration of the dementing process (Niccoli & Partridge, 2012; Tadic, Cuspidi, & Hering, 2016*;* Canet, Chevallier, Zussy, Desrumaux, & Givalois, 2018; Liu, Zhang, Xi, Zhao, Wang, Wang *et al.*, 2018; Legdeur, van der Lee, de Wilde, van der Lei, Muller, Maier *et al.*, 2019). Other important factors, which are less known and less caught, seem to be chronic depression, untreated depression and history of previous head trauma. All these factors significantly inhibit cellular activity at different cerebral regions, mainly at the hippocampal level (Liu, Yu, Wang, Han, Tan, Wang *et al.*, 2015; Wang, Yuan, Pang, Ma, Han, Geng *et al.*, 2016; Haller, Montadon, Rodriguez, Garibotto, Liljia, Hermann *et al.*, 2019).

Other factors contributing to the pathogenesis of Alzheimer's disease are traumatic brain injuries (Edwards, Gamez, Escobedo, Calderon, & Moreno-Gonzalez, 2019), the presence of thyroid dysfunctions (Bavarsad, Hosseini, Hadjzadeh, & Sahebkar, 2019; Nomoto, Kinno, Ochiai, Kubota, Mori, Futamura *et al.*, 2019), repeated exposure to general anesthesia (Kline, Pirraglia, Cheng, De Santi, Li, Haile *et al.*, 2012; Eckenhoff & Laudansky, 2013; Yang & Fuh, 2015; Schenning, Murchison, Mattek, Silbert, Kaye, & Quinn, 2016; Bratzke, 2018) and abnormal neuroimmune disorders (Zappalà, 2019).

Events occurring during the early phases of life, although often neglected, seem to alter the course of brain development, representing the basis for post-natal stages and future anatomical, physiological and behavioral outcomes. It has been shown that some specific genes change

their expression during fetal and early postnatal development and affect neuronal processes throughout life, playing a possible role in the etiology of the neurodegenerative process (Babenko, Kovalchuk, & Metz, 2014; Nalivaeva, Turner, & Zhuravin, 2018). Birth stress, such as premature birth, hypoxia, maternal age at birth, low birth weight, perinatal brain injury all have a role in the development of the cerebral nervous system (Thompson, Warfield, Carlin, Pavlovic, Wang, Bear *et al.*, 2007). Studies in non-human primates have described how fetal exposure to stress and prenatal stress produce alterations in hippocampal plasticity due to the higher level of glucocorticoids with consequences during the life-span (Coe, Kramer, Czèh, Gould, Reeves, Kirschbaum *et al.*, 2003; Lemaire, Lamarque, Moal, Piazza, & Abrous, 2006; Sandman & Davis, 2010).

The impact of events that occur during pregnancy and early life are strongly associated with the remodulation and reorganization of hemispheric specialization, manual preference and cognitive competence. According to the Geschwind-Behan-Galaburda (GBG; Geschwind & Behan, 1982; Geschwind & Galaburda, 1985) hypothesis higher prenatal and post-natal levels of testosterone are directly linked with "anomalous" hemispheric lateralization. High intrauterine levels of testosterone produce a reduced growth of maturation of the language areas on the left side of the brain, which leads to some right hemisphere language competence and left-handedness (Stoyanov, Decheva, Pashalieva, & Nikolova, 2012). Furthermore, testosterone produces thymus dysfunction, leading to immune dysfunctions and other disorders (Geschwind & Galaburda, 1985). Perinatal brain injury or low birth weight in infants are correlated to the subsequent preference of "anomalous" left or mixed handedness (Bakan, 1971; O'Callaghan, Burn, Mohay, Rogers, & Tudehope, 1993; McManus, 1995; Annett, 2002; Heikkila, Van Bejsterveldt, Haukka, Livanainen, Saari-Kemppainen, Silventoinen *et al.*, 2018). Rodriguez & Waldenstrom (2008) also reported that prenatal experience of maternal depression or critical life events were associated with atypical handedness (*left, mixed and non-right handedness*) of children. Moreover, the presence of familial left-handedness was shown to increase the percentage of left-handedness (Porac, 2016). As the literature suggests, genetic variants of left-handed individuals contribute to the neurodevelopmental lateralization of brain organization, which influences manual preference and the predisposition to develop neurodegenerative and psychiatric diseases (Shimizu, Endo, Yamaguchi, Torii, & Isaki, 1985; Siebner, Limmer, Peinemann, Drzezga, Bloem, Schwaiger *et al.*, 2002; Meng, 2007; Kloppel, Mangin, Vongerichten,

Franckowiak, & Siebner, 2010; Stoyanov, Nikolova, & Pashalieva, 2011; Wiberg, Michael, Al Omran, Alfaro-Almagro, McCarthy, Marchini *et al.*, 2019).

The role of anomalous manual preference and hemispheric specialization, which occurs since birth, has not been thoroughly studied thus far on aging and cognitive decline, while it has been investigated thoroughly in intellectual disability, learning disturbances and other diseases (e.g., Pipe, 1990; Coren & Halpern, 1991; Eglinton & Annett, 1994; Di Nuovo & Buono, 2003).

Ontogenetically speaking, brain asymmetry and manual preference start developing since the very early phase in the fetus and are continuously remodulated and reorganized depending on various genetic and environmental factors. Hand preference is directly associated with brain organization and the degree of functional asymmetries of all neuropsychological functions (Coren, 1992; Stroganova, Pushina, Orekhova, Posikera, & Tsetlin, 2004).

Approximately 95% of right-handers have the language centers represented on the left hemisphere, but 70% of left-handers also do. However, “atypical right-handedness” has been more frequently linked to bilateral or right hemisphere dominance for language processing (Steinmetz, 1996; Pujol, Deus, Losilla, & Capdevila, 1999; Knecht, Drager, Deppe, Bobe, Lohmann, Floel *et al.*, 2000; Szaflarski, Binder, Possing, McKiernan, Ward, & Hammeke, 2002; Sommer, Aleman, Somers, Boks, & Kahn, 2008; Corballis, 2012; Nenert, Allendorfer, Martin, Banks, Holland, & Szaflarski, 2017). Moreover, cultural, geographic, and religious beliefs have historically influenced people’s autonomous selection of their preferred hand for many centuries. Left-handed or “ambidextrous” individuals have been forced to shift to the right-hand preference, contrasting their “natural” skills (Porac, 2016).

Decades ago, left-hand preference represented the "*devil's hand*", a negative trait which could not be permitted during the course of childhood and teenage growth. Forcing the shift to the “right” hand did not have a beneficial effect on the cognitive abilities of the people involved, who were actually forced to reorganize and redistribute the brain through complex behaviors. Hemispheric representation became improperly “equalized” and linguistic as well other cognitive abilities were reinterpreted. Changing somebody’s hand in the very early phase of development brought to reduced competence, diminished linguistic skills and, maybe, to reduced mnestic skills during the aging process. These changes were based on

structural and connection network anomalies, which, in turn, with aging, could lead to "word-search" difficulties, reduced verbal fluency and learning disabilities, especially in older individuals who today come to our clinical settings for a cognitive assessment. Rasmusson and co-workers (1996) reported that "non-right handedness" is a factor predicting a more rapid decline, as measured through the Mini-Mental State Examination (MMSE).

The convergence of all these reported factors (starting very early from birth) reduces the physiological "resilience" of the brain system. Cognitive decline starts to emerge ahead of time with aging. Brain resilience as a "cognitive reserve" mechanism is a compensatory process that reduces the impact of aging upon cognitive capacities (Livingston, Sommerlad, Orgeta, Costafreda, Huntley, Ames *et al.*, 2017). The early reorganization of language and cognitive skills due to a profound redistribution of skills and the specialization of each hemispheric competence secondary to the "change of hand preference" becomes a suspicious and significant factor of pathological aging with a significant impact on one's cognitive reserve and physiological resilience (Zappalà, 2019).

In summary, the "changes" of cerebral organization and manual preference could be considered "epigenetic risk factors", which occur early on during the development of brain organization and cognitive competence. The convergence of all the mentioned factors (during fetal development, childhood, and throughout mid and late-life) negatively influence the resistance of the brain apparatus (resilience) and cognitive symptoms start to emerge. If they remain under-reported and less investigated, such deviant processes may continue to impact upon the level of cognitive activity, which, in turn, reduces concentration, short-term memory, confidence, and general activity, building up a pathological loop of extreme severity, if left undiagnosed (Zappalà, 2019).

2. Aims of study

The aim of the present study was to explore the prevalence of right-handers and non-right handers in a sample of subjects with different levels of cognitive decline, through descriptive and correlational analyses. More specifically, the individuals assessed as "forced right-handers" (i.e., having been forced to change their handedness from left to right) were taken into account with the aim of analyzing the possible relationship with the levels

of cognitive deterioration. The incidence of familial left-handedness was also explored.

3. Methods

3.1. Participants

The sample was composed of 246 subjects of which: 109 males (44.31%), 137 females (55.69%), with a mean age of 73.24 years old, *SD* = 8.50, and a mean of years of education of 10.18, *SD* = 5.18.

The subjects enrolled in the study were all outpatients of a Cognitive Neurology and Dementia Services Department. All subjects reported cognitive decline, such as short-term memory loss, concentration deficits, naming troubles, and disorientation in time and space. They also reported initial difficulties in social behavior and tendency to be socially withdrawn. Subjects were stratified for their severity of cognitive decline. Most of them were labeled as mild (*N* = 115), others as moderate (*N* = 75) or severe (*N* = 56) according to current clinical diagnostic criteria and MMSE score (see Instruments section below). Patients who had symptoms probably associated with other diagnostic pathologies, such as multiple sclerosis, traumatic brain injury and/or stroke, were excluded from the study.

3.2. Instruments

- The Italian version of the Mini-Mental State Examination (MMSE) was used to measure the level of cognitive decline (Measso, Cavarzeran, Zappalà, Lebowitz, Crook, Pirozzolo *et al.*, 1993; Grigoletto, Zappalà, Anderson, & Lebowitz, 1999). The test consists of 12 items with verbal and performance tests exploring different functions: temporal and spatial orientation, short-term memory, recall, attention, and calculation, language and visual-constructive praxis. The score obtained is corrected for age and educational level and the cut-off value is 23.8/30. In this study, scores between 23.8 and 27 were diagnosed as mild cognitive decline, below 23 as moderate cognitive decline and 17 and less as severe cognitive decline.
- In addition to the MMSE, the Montreal Cognitive Assessment (MoCA; Nasreddine, Philips, Bédirian, Charbonneau, Whitehead, Collin *et al.*, 2005; Santangelo, Siciliano, Pedone, Vitale, Falco, Bisogno *et al.*, 2014) was administered to a subset of the total sample

(*N* = 73, with mean age = 69.03, *SD* = 8.34; mean of years of education = 12.01, *SD* = 5.76), as it is more discriminant for the diagnosis of mild impairment in the borderline conditions as highlighted by the MMSE scores. On the MoCA, the cognitive domains evaluated are executive functions, attention and concentration, spatial-visual skills, language, working memory and recall and orientation. The cut-off is 26/30 and scores above or equal to this are considered normal; correction for the level of instruction is also included.

- Manual preference was classified by means of a *Laterality Index* for the preferred hand (Salmaso & Longoni, 1985) integrated for clinical use with older subjects (Zappalà, 2019). The administration and scoring for the definition of the preferred hand is based on a guided interview and/or actual performance on 15 commonly used items in daily life. The index allows to detect the left-handers (score < 20) from forced right-handers (scores 20-32) and genuine right-handers (score > 32).
- Finally, the left-handedness of at least one of the patients' immediate relative was explored by an anamnestic interview used as a routine in the Cognitive Neurology Laboratory. This information was obtained for *N* = 199 patients (i.e., 80.89% out of the total sample).

4. Results

Descriptive and correlational analyses were performed through both parametric and nonparametric techniques (for classification tables) using the statistical software SYSTAT v. 13.2.

A preliminary analysis compared the proportion of handedness in men and women (Tab. 1). Forced right-handers were prevalent in men, who had fewer left-handers than women, although the difference was not statistically significant ($\chi^2 = 3.84$, $p > .05$).

Table 1 – *Proportion of right, left, and forced right-handers in men and women*

	Men (n = 109)	*Women (n = 137)*	*Total (n = 246)*
Right-handers	47 (43.12%)	62 (45.25%)	109 (44.31%)
Left-handers	13 (11.93%)	27 (19.71%)	40 (16.26%)
Forced right-handers	49 (44.95%)	48 (35.04%)	97 (39.43%)

$\chi^2 = 3.84$, $df = 2$, $p = .15$

The following analysis regarded the whole sample with cognitive decline (N = 246): based on the data reported in Table 1, 44.31% of the patients were right-handers, 39.43% were forced right-handers and 16.26% were left-handers (total non-right handedness 55.69%). In the general population, left-hand preferences range from 7.9% to 15.4%, with a mean of 9.2% (Papadatou-Pastou, Ntolka, Schimitz, Martin, Munafo, Ocklenburg *et al.*, 2020). Porac (2016) reported that in Southern Italy (from where our sample was recruited), the prevalence of left-handers is reduced to about 5%; this may depend on the cultural prejudice towards left-handedness forcing right-handedness in the earlier stages of development. However, the percentage of non-right-handers in our sample of older people with cognitive impairment was significantly different from the general population (both assuming it at 9% or at 15%: binomial test, $p < .001$). The high prevalence of non-right-handers among the individuals with early signs of cognitive decline and dementia, which was significantly higher than expected in the general population, was thus considered striking.

The difference among the categories of handedness was non-significant ($F_{2,243} = .91$, $p = .40$) as shown by the MMSE scores. In fact, the MMSE mean score in right-handers = 21.81 (SD = 5.12), in left-handers = 22.43 (SD = 5.06) and in forced right-handers = 22.77 (SD = 1.97).

No statistical significance emerged even when the rate of handedness among subjects was correlated to their different levels of cognitive decline (see Tab. 2 below).

Table 2 – *Manual preference in the different levels of cognitive decline*

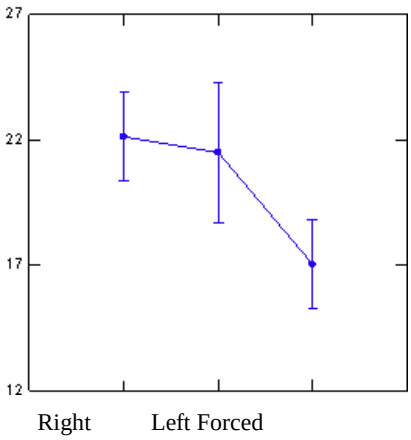
	Cognitive Decline			
	Mild (*n = 115*)	*Moderate* (*n = 75*)	*Severe* (*n = 56*)	*Total* (*n* = 246)
Right-handers	48 (41.7%)	34 (45.3%)	27 (48.2%)	109 (44.3%)
Left-handers	20 (17.4%)	10 (13.3%)	10 (17.9%)	40 (16.3%)
Forced right-handers	47 (40.9%)	31 (41.3%)	19 (33.9%)	97 (39.4%)

$\chi^2 = 1.51$, $df = 4$, $p = .82$
Note: MMSE mean for levels: Mild = 25.54; Moderate = 20.17; Severe = 12.36.

In contrast, when the handedness preference was correlated to the MoCA scores the results were statistically significant (ANOVA, $F = 9.05$, $p < .001$). As is depicted in Figure 1, the performance on MoCA was lower in forced right-handers (M = 17.03, SD = 4.87) than in left-handers (M = 21.50, SD = 5.22) and in right-handers (M = 22.13, SD = 4.90). The MoCA test, which is more appropriate for the assessment of Mild Cognitive

Impairment than the MMSE, was able to reveal the differences in this specific sub-sample more effectively.

Figure 1 – *Difference of mean MoCA score for manual preference in the subsample of Mild Cognitive Impairment*



Finally, familial manual preference was explored for a subsample, as previously described in the Methods section. For 93 cases it was confirmed that at least one immediate relative was a left-hander or had been forced to use the right hand although being originally left-handed. Table 3 shows that left hand preference was more incident among immediate relatives of left-handed subjects (a total of 22.6 % vs 6.73% right handers). Among the forced right-handers, 51.6% (half of the subjects) had familiar left-handedness. Table 3 thus shows that when subjects' manual preference was compared to familiar handedness the results were significant ($\chi^2 = 26.48$, $p < .001$).

This very high incidence of familiarity of leftward manual preference was found to be significantly linked with the severity stage of cognitive impairment in the sons/daughters ($\chi^2 = 5.82$, $p = .05$; see Tab. 4). A strong association between lateral preferences in the patients and their parents was reported and this association appeared to increase proportionally with the patients' cognitive level (43% in Mild, 33% in Moderate, 17% in Severe impairment). For half of MCI patients familial left-handedness was reported.

Table 3 – *Relationship between subjects' manual preference and familiar handedness*

	Familiar handedness		
Subject's handedness	*Right*	*Left*	*Total*
Right-handed	64 (60.4%)	24 (25.8%)	88 (44.2%)
Left-handed	7 (6.6%)	21 (22.6%)	28 (14.1%)
Forced right-handed	35 (33.0%)	48 (51.6%)	83 (41.7%)
Total	106	93	199

$\chi^2 = 26.48$, $df = 2$, $p < .001$

Table 4 – *Familial manual preference on subjects with different level of cognitive impairment*

	Cognitive Decline			
	Mild	*Moderate*	*Severe*	*Total*
No familial left-handedness	43 (21.61%)	28 (14.07%)	35 (17.59%)	106 (53.27%)
Familial left-handedness	43 (21.61%)	33 (16.58%)	17 (8.54%)	93 (46.73%)

$\chi^2 = 5.82$, $df = 2$, $p = .05$

5. Discussion

Neurodegenerative disease is an atypical way to aging, with relevant consequences on social and health policies. The presence of specific genetic and epigenetic predictive factors increases the risk of pathological cognitive decline. All events occurring from the earliest days of life and during the life span of an individual can contribute to change brain organization and cognitive competence. Cognitive derailment with aging is a common event among individuals older than 60 years of age. The current literature focuses on risk factors and predictive comorbidities, mostly vascular factors, which impact on brain's health and its lower resilience with aging. However, lately also genetic and epigenetic factors have been explored more intensively, among which neuro-immunitary frailties, general anesthesia during surgeries (due to neuroinflammation processes), traumatic head injury, low education and scarce psychosocial involvement. A deep and thorough history of the early phases of brain development and the role of language competence and hand preference have not been appropriately investigated, to the best of our knowledge. Their relationship to cognitive decline, memory disturbances and naming difficulties has not been properly explored during early screening and assessment of cognitive decline associated with aging, including dementia.

Our study explored the relationship between the presence of "non-right handedness" (forced or not) and severity of cognitive decline in old people, through both a descriptive and correlational analysis. The results show that in all three degrees of cognitive impairment (mild, moderate and severe) there was a prevalence of non-right handers; this result was significantly different from the expected percentage of the general population in which the prevalence of left-handers does not exceed a percentage of 15% (Papadoutou-Pastou *et al.*, 2020).

The analysis of variance showed a statistically significant difference of mean scores on the MoCA test between severity of cognitive decline and anomalous manual preference, whereas the same results were non-significant when using the most common Mini-Mental State Examination. This might be due to the increased sensitivity, specificity and accuracy of the MoCA test for screening cognitive decline and non-Alzheimer's dementia rather than the MMSE (Hoops, Nazem, Siderowf, Duda, Xie, Stern *et al.*, 2009; Freitas, Simões, Alves, Duro, & Santana, 2012; Freitas, Simões, Alves, Vicente, & Santana, 2012; Trzepacz, Hochstetler, Wang, Walker, Saykin, & Alzheimer's Disease Neuroimaging Initiative, 2015).

Familial history of left-handedness among subjects diagnosed with cognitive decline was very high, reaching 46.73% of the total sample.

In conclusion, our results confirmed the prevalence of non-right handers, who corresponded to more than half of our sample with cognitive decline, without differences in the levels of severity. Forced right-handers represented the majority both in mild, moderate, and severe stages. Other studies have also indicated a similar association between non-right handers with cognitive disorders in the semantic variant of primary progressive aphasia (Miller, Mandelli, Rankin, Henry, Babiak, Frazier *et al.*, 2013).

Our emphasis on the high prevalence of individuals with non-right hand preference derives from the consideration that brain organization and cognitive competence develops differently among right- and left-handers, not only for linguistic competence but also for memory strength and social-emotional skills. Pathological aging and dementia represents a long trail of decay. Most individuals begin to show initial signs of cognitive deterioration very early on during their mature age. Whereas factors, such as hypertension, cholesterol level and the diameter of brain vessels, have all been rigorously investigated during the last decades, other epigenetic factors, such as brain organization, linguistic competencies, cognitive styles and hand preferences have received less attention. The aim of our approach, instead, was to cover and thoroughly explore the early derailments of

cognitive strength during the assessment phase leading to a diagnosis of cognitive decline and/or dementia. This paper adds evidence for a direct correlation between manual preference, i.e. non-right preference (particularly if forced to right by education), and the development of early signs of dementia.

6. Limitations and conclusions

The current study represents an attempt to investigate "epigenetic factors" influencing the prodromal stages of cognitive decline. However, the recruited subjects were a convenience sample of individuals who were diagnosed at our Cognitive neurology section, all in the same hospital site. Therefore, this sample cannot be defined as representative of the general population considered.

Moreover, the analysis of the relatives' handedness was based on a retrospective report, which was not possible for all the participants but only a subsample of our dataset.

Another limitation could be represented by the descriptive and correlational analyses since it was not possible – due to the characteristics of the sample - to perform multivariate analyses.

Notwithstanding, the study should be considered a preliminary exploration of the prevalence of non-right handers, including "forced right-handers", along the aging process, and the relationship with different levels of cognitive deterioration.

In the future, the study of laterality of manual skills might be an easy and direct route to investigate the patterns of cognitive decline associated with aging. The aging brain becomes vulnerable from the very early stages of life, not only when our age reaches mature competence. Taking in consideration an evolutionary approach to history taking and cognitive assessment during cognitive decline could help uncover seemingly less significant elements, such as manual preference in addition to other well-known factors already mentioned. This might be a useful approach to prevent the vulnerable nature of neurodegenerative diseases by planning interventions at their earliest stages of development.

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