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

Febronia Riggio, Santo Di Nuovo & Giuseppe Zappalà

The impact of COVID-19 confinement on the neurobehavioral manifestations of people with Major Neurocognitive Disorder and on the level of burden of their caregivers

Simonetta Panerai, Giuseppina Prestianni, Sabrina Musso, Stefano Muratore, Domenica Tasca, Valentina Catania, Donatella Gelardi & Raffaele Ferri
Examining determinants of Metabolic Syndrome in people with Intellectual Disabilities

Ram Lakhan¹, Vinayak K. Nahar²,³, Louisa Summers¹ & Manoj Sharma⁴

Abstract

Introduction: There is growing evidence of an increased risk of Metabolic Syndrome (MetS) in people with Intellectual Disabilities (ID). It is an emerging public health issue. People with ID are particularly vulnerable to the negative sequelae of MetS. Due to the slower learning process, people with ID find it difficult to regulate their dietary habits. Determinants of MetS in this population have not been adequately explored, which is the purpose of this study. Objectives: To identify the determinants of metabolic syndrome in people with intellectual disabilities. Methods: A comprehensive literature search was conducted in MEDLINE (PubMed), CINAHL, and Google Scholar. The following inclusion criteria were used in the selection of the articles: (1) published within the past 10 years; (2) published in the English language; (3) published in peer-reviewed journals; (4) original research concerning MetS including descriptive, epidemiological studies, and (5) focus on ID. Grey literature was not included in the search. Results: A total of nine

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studies met the inclusion criteria. Studies were found to have higher rates of MetS in the order of 25% to 45% in people with ID. Physical inactivity, sedentary lifestyle, living independently in community settings, having the ability to prepare meals, being a woman, lacking access to health education programs, deficiencies in the awareness concerning health as well as the reduced opportunities of engaging in cognitive activities, especially among older-aged women, were found as the major determinants of MetS in ID populations. Conclusions: This study provides insights into certain determinants of MetS in the ID population, which has been neglected in the literature, to the best of our knowledge. Our hope is that interventions can be planned and implemented with ID populations based on the evidence, as highlighted in this study.

Keywords: Intellectual Disability; Metabolic Syndrome; Determinants.
1. Introduction

Metabolic syndrome (MetS) is considered a global epidemic (Saklayen, 2018) and a serious threat to public health (Bankoski, Harris, McClain, Brychta, Caserotti, Chen et al., 2011). MetS is a cluster of diseases. It happens when any three or more conditions out of five including abdominal obesity, elevated blood pressure, elevated blood glucose levels, low high-density lipoprotein cholesterol (HDL-C), and elevated triglycerides meet together (Cornier, Dabelea, Hernandez, Lindstrom, Steig, Stob et al., 2008). According to the definition, abdominal obesity is considered when the waist circumference is equal or more than 40 inches in men and 35 inches in women, blood pressure values are equal or over 130 mmHg systolic and 85 mmHg diastolic, elevated fasting glucose is over 100 mg/dL, HDL-C is 40mg/dL in men and 50 mg/dL in women and elevated triglycerides present a value that is 150 mg/dL or greater (Huang, 2009). Estimates suggest that 11 million deaths can be attributed to metabolic syndrome (MetS), on an annual basis, worldwide (Danaei, Lu, Singh, Carnahan, Stevens, Cowan et al., 2014). The burden of MetS in intellectual disabilities is also increasing. The link between MetS and chronic diseases, including cardiovascular disease, diabetes, arthritis, chronic kidney disease, schizophrenia, and several types of cancer has already been established (Goldberg & Mather, 2012). MetS is also found to be associated with early death (Mottillo, Filion, Genest, Joseph, Pilote, Poirier et al., 2010; Moore, Chaudhary, & Akinyemiju, 2017). The risk of MetS can be reduced substantially by making lifestyle changes (Yamaoka & Tango, 2012). However, it is very difficult for people to make such changes in their lifestyle. The challenge of making lifestyle changes in people with ID is multiple times higher than non-ID people because of their low level of processing skills, behavioral problems, less education and awareness regarding health, high sensitivity towards immediate smaller rewards, and low ability of managing things in their lives (Carmeli, Zinger-Vaknin, Morad, & Merrick, 2005; Lakhan, Sagiraju, Ekündayò, & Sharma, 2019). In recognition of the increasing rate of MetS in all populations, it is imperative that the risk and its negative consequences on health should be studied in the ID population. Determinants of MetS in this section of the population have not been adequately explored, which is the purpose of this study.
2. Objective

The purpose of this study was to identify and discuss determinants of MetS in people with Intellectual Disabilities.

3. Methods

A comprehensive literature search was conducted in MEDLINE (PubMed), CINAHL, and Google Scholar. The following inclusion criteria were used in the selection of the articles: (1) published within the past 10 years; (2) published in the English language; (3) published in peer-reviewed journals; (4) original research concerning MetS including descriptive, epidemiological studies, and (5) focus on ID. The search was conducted with the following two keywords: intellectual disability and metabolic syndrome; mental retardation and metabolic syndrome. We found 15 studies in MEDLINE (PubMed), one in CINAHL, and nine in Google Scholar. After a careful reading of the 25 titles, 6 articles that appeared in our search were excluded as they were duplicate titles and 19 papers were found to be relevant so that their abstracts were read more thoroughly. Ten articles, out of 19, were further excluded for the following reasons: four articles did not cover three components of MetS, five articles used ID as a secondary disability and the last article focused its attention on Prader-Willi Syndrome (please see Fig. 1 for more details).

4. Results

A total of nine studies met the inclusion criteria and looked at the social determinants behind MetS in the ID population. Three studies were conducted in The Netherlands and one each in China, Italy, Sweden, South Korea, Taiwan, and the United Kingdom. Seven studies followed a cross-sectional research design, two analyzed secondary data, and one used a mixed methods design. Studies were found to have higher rates of MetS in the order of 25% to 45% in people with ID. In this review, the major factors determining MetS in people with ID were found to be physical inactivity (30% of studies), the living setting (20%), gender (10%), age (10%), low levels of health education and awareness (10%) and multiple factors (10%), including the use of conventional antipsychotic drugs, age, and low nutrition. Interestingly, one study observed a better outcome of MetS in
terms of better cognitive function in the older female ID population (refer to Tab. 1 for more details).

Figure 1 – Flow diagram of the literature search process

5. Discussion

The objective of this study was to identify the determinants of metabolic syndrome (MetS) in the intellectually disabled population through a review of the literature. Several determinants were identified in this review.

Two studies conducted in South Korea (Kim & Yi, 2018) and the United Kingdom (Harris et al., 2018) demonstrated that MetS in people with ID may be due to physical inactivity. Physical inactivity is defined as the lack of moderate to vigorous physical activity and is also called as sedentary behavior. It is a serious concern among all people but seems to be even more important in people with ID and is one of the main modifiable risk factors for MetS (Park, Park, Togo, Watanabe, Yasunaga, Yoshiuchi et al., 2008).
Table 1 – *Studies included in the review*

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Year</th>
<th>Research design</th>
<th>Population, sample size, and age</th>
<th>Significant findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laudiaco, Marzetti, Paganò, Cocchi, Franceschini, Bernabei, &amp; Zucalà</td>
<td>Italy</td>
<td>2008</td>
<td>Cross-sectional</td>
<td>353 People with ID age ≥ 75 years old</td>
<td>MetS was found to be associated with a better cognition performance in the older female population (p &lt; .01)</td>
</tr>
<tr>
<td>Wallén, Mållersdorf, Christenson, Malm, Ekblom, &amp; Marcus</td>
<td>Sweden</td>
<td>2009</td>
<td>Cross-sectional</td>
<td>66 students enrolled in secondary schools and 90 without ID were recruited in the study</td>
<td>Prevalence of cardio-metabolic risk was found to be high in young people with intellectual disabilities</td>
</tr>
<tr>
<td>de Winter, Magaïsa, van Alfen, Willensma, &amp; Evenhuis</td>
<td>The Netherlands</td>
<td>2010</td>
<td>Cross-sectional</td>
<td>470 adults with ID were examined in the study, age ≥ 50 years old, living in residential organizations</td>
<td>Metabolic syndrome was 25.1% [95% CI 21.0 - 29.3%]. It had a significantly higher risk in people with mild ID</td>
</tr>
<tr>
<td>Hsu, Yen, Hung, Lin, Wu, &amp; Lin</td>
<td>Taiwan</td>
<td>2012</td>
<td>Cross-sectional</td>
<td>164 people with ID with a mean age of 20 years old were recruited in the study, living in institutions</td>
<td>Prevalence of MetS was found to be 11.6% (8% in males and 17.2% in females). This was lower than that in the general population of Taiwan. OR = 3.83, 95% CI [1.98 - 7.41]</td>
</tr>
<tr>
<td>de Winter, Bastiaarse, Hilgenkamp, Evenhuis, &amp; Echteld</td>
<td>The Netherlands</td>
<td>2012</td>
<td>Cross-sectional</td>
<td>980 people with borderline to profound ID</td>
<td>The rate of MetS was found to be 44.7%. People who lived more independently and people who were able to do groceries or prepare a meal independently had higher risk for MetS 44.3%, 95% CI [40.7% - 48.7%].</td>
</tr>
<tr>
<td>Reema, Timmerman, &amp; Roodbol</td>
<td>The Netherlands</td>
<td>2016</td>
<td>Mixed-methods design</td>
<td>Medical records of people with and without IDs of a Dutch health care institute were examined</td>
<td>A mixed-methods research design was applied. Medical data and laboratory exams were analyzed for 260 people with ID MetS in people with IDs was found to be 46%. Conventional antipsychotic drugs (2.4 times [95% CI 1.246 - 4.747]) age, and low nutritional score were found to be associated with MetS</td>
</tr>
<tr>
<td>Kim and Yi</td>
<td>South Korea</td>
<td>2018</td>
<td>Cross-sectional</td>
<td>A total of 17 people (13 men and 4 women) with ID from 18 to 60 years of age, IQs between 12 to 70</td>
<td>Physical inactivity was found to be a significant factor of high metabolic rate (p &lt; .05)</td>
</tr>
<tr>
<td>Harris, McGarty, Hilgenkamp, Mitchell, &amp; Melville</td>
<td>UK</td>
<td>2018</td>
<td>A secondary analysis of data from two randomized controlled trials of lifestyle behavior changes was conducted</td>
<td>143 people with ID</td>
<td>Sedentary behavior was found to be significantly associated with a higher risk of MetS (p &lt; .05)</td>
</tr>
<tr>
<td>Wang, Wong, Taylor-Pilase, Qiu, &amp; Li</td>
<td>China</td>
<td>2019</td>
<td>Cross-sectional</td>
<td>204 people aged 58.5 ± 10.1 years (55% males)</td>
<td>A low level of knowledge and lack of specific health education were found to be associated with MetS (p &lt; .001)</td>
</tr>
</tbody>
</table>
According to the 2003 to 2006 National Health and Nutrition Examination Survey (NHANES) data analysis, people with MetS spend about 67.3% of their time in sedentary behavior (Bankoski et al., 2011). People with ID usually do not hold jobs like most other people in society. If they are not provided with adequate options for staying physically active they tend to become sedentary, which contributes to MetS.

Interestingly, two studies, which were both conducted in The Netherlands, seemed to be in contrast to the previous findings since they reported the living setting to be associated to a higher risk of MetS in people with ID, especially in patients living in a residential setting and having a mild level of ID (de Winter et al., 2010) as well as in individuals living more independently and that were also more likely to purchase groceries and to cook their meals on their own (de Winter et al., 2012). Other studies conducted in the ID population reported that the rate of obesity was higher among those who were older, had less severe ID, were more independent in eating by themselves and were more independent in doing their groceries and cooking their food by themselves (Melville, Hamilton, Hankey, Miller, & Boyle, 2007; Maiano, 2011; Hsieh, Rimmer, & Heller, 2014).

Moreover, people with ID and characterized by a lower level of health education, knowledge, and awareness were found to be more associated with MetS in a study conducted in China (Wang et al., 2019). However, a similar association between a low level of health education and MetS was also observed in the non-ID population (Ramsey & Glenn, 2002).

These findings assume that researchers are referring to people with an ID severity that is less pronounced and that, thus, present a certain capacity for understanding health education and its implications. If this inference is correct then it means that people with less severe ID are more independent in making dietary choices and, as a result, they are more subject to a higher rate of obesity and a consequent higher risk of MetS. Thus, if on the one hand, people with less severe ID are likely to be less sedentary, since they are able to buy their groceries and cook their meals on their own, on the other hand, the fact of being able to make dietary choices of their own makes them more vulnerable to obesity and, consequently, to MetS.

One study found female gender to be highly associated with a higher risk of MetS in people affected by ID (Hsu et al., 2012). This finding was consistent with studies conducted in the non-ID population that demonstrated a higher association between MetS and female gender (Beigh & Jain, 2012; Aguilar, Bhuket, Torres, Liu, & Wong, 2015).
Age was also found to be strongly correlated to a higher risk of MetS in the non-ID population (Aguilar et al., 2015). In our dataset, only one study conducted in Sweden examined the relationship between age and MetS (Wallén et al., 2009). A further paper, instead, which was conducted in The Netherlands, examined the relationship between age and MetS with another ID factor, the intelligence quotient (IQ), reporting that the rate of MetS in the ID population increased with age (de Winter et al., 2012). This can be explained by the fact that people with ID might experience a much greater risk of MetS correlated to age because often adult people with ID lack employment opportunities and live an inactive life, as opposed to their age-matched adults (Khayatzadeh-Mahani, Wittevrongel, Nicholas, & Zwicker, 2019). In fact, in most places children with ID attend some form of school, just like non-ID children, and receive opportunities to engage in various activities but once they cross this school age, they often do not obtain a job like their age-matched non-ID peers, which limits their participation and scope of staying active due to a life set by a fixed routine.

In a mixed-methods research design, conducted in The Netherlands, the researchers found a higher association between the use of conventional psychotropic drugs and MetS in people with ID (Room et al., 2016). A similar association between psychotropic drugs and MetS, however, was also reported for the non-ID population (McIntyre, Park, Law, Sultan, Adams, Lourenco et al., 2010).

MetS was also observed to be often associated with a poor cognitive function in elderly of the non-ID population (Panza, Frisardi, Capurso, Imbimbo, Vendemiale, Santamato et al., 2010; Yates, Sweat, Yau, Turchiano, & Convit, 2012). A study conducted by Laudisio and colleagues found a better cognitive outcome of MetS in older ID women in Italy (Laudisio et al., 2008). Learning more about the implications of MetS on the cognitive functioning in people with ID could be an area of research that should be further investigated.

In conclusion, when it comes to non-modifiable risk factors, including age and gender, and to modifiable risk factors, such as the use of conventional psychotropic drugs and physical inactivity, the association of these factors and MetS was found to be similar in the ID population compared to the non-ID population. However, people with a mild ID severity who were thus relatively independent in eating and preparing their food, and in living either in residential facilities or living independently in community settings, presented a higher risk of MetS compared to the non-ID population since their independence in making dietary choices was
unfortunately correlated to lower levels of health education, knowledge, and awareness, making them more subject to obesity and, thus, to MetS.

6. Limitations and Strengths

This study has a few limitations, including the fact that the search was conducted only through three databases. Moreover, articles published in other languages other than English were not included. Most of the studies included in this review came from European countries, North America, and South Asia. In fact, we were not able to find any peer-reviewed studies on this topic from the Indian subcontinent, Middle East Asia, Africa, South America, and Australia. In addition, the living conditions and health and rehabilitation services for people with ID vary from nation to nation. Lack of such material makes the findings of this review less generalizable for the ID population across the world. Notwithstanding, our work is unprecedented, to the best of our knowledge, and is the first study attempting to summarize the findings reported in the literature concerning the determinants of MetS in the ID population. We were also able to highlight here a better cognitive outcome of MetS in older ID women in Italy.

7. Conclusions

This study provides insights into certain determinants of MetS in the ID population, which has been a neglected topic, until now, as far as we know. Our hope is that interventions can be planned and implemented with ID populations based on the evidence, as highlighted in this study.

References


Music-dance-imaging training for young adults with Tourette Syndrome

Carlotta Zanaboni Dina¹, Sabrina Rago¹, Alice Cancer¹
 & Alessandro Antonietti¹

Abstract

Tourette Syndrome (TS) is a childhood-onset neurobehavioral disorder, which is characterized by motor and sound tics. Current studies have identified some specific factors that lead to tic reduction, such as relaxation, concentration, musical activities, and the execution of voluntary and finalistic movements. Patients with TS show a higher level of creativity than other people, which can be channeled, together with their excessive motor energy, into various functional activities that favor the reduction of tics. Moreover, in the last decades, music has been used as a rehabilitative tool, since it has shown to induce a positive effect on TS patients’ mood and to facilitate the performance of fluid and rhythmic voluntary movements. The present study refers to “Imagine, Tourette!”, a motor imagery, music-based intervention aimed at reducing the manifestation of motor and sound tics in adult TS patients. To test the specific effect of such a kind of training, 8 TS patients were exposed to one of two interventions: the experimental group performed motor tasks based on music whereas the control group performed motor tasks without the accompaniment of music. The hypothesis tested was that performing motor tasks accompanied by music could reduce the severity of tics and have an effect on patients’ mood more than simply performing motor

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tasks alone. The results supported the hypothesis: music played a specific effect on the manifestation of tics and on the patients’ mood, confirming its potentially positive role in motor interventions addressed to TS.

Keywords: Tourette; Tic; Music; Music Therapy; Dance; Voluntary movement; Imaging; Mood; Training.
1. Introduction

Tourette Syndrome (TS) is a childhood-onset neurobehavioral disorder, which is characterized by motor tics and at least one sound tic (American Psychiatric Association, 2013). Tics are repetitive, arrhythmic, semi-voluntary, and bring to non-finalistic movements. TS is a common syndrome (1% of the general population) with a complex etiology, which is mostly genetic and infective. Most patients (90%) present comorbidities with psychopathologies, including depressive symptoms as well as a reduced quality of life (Robertson, 2011; Zanaboni Dina & Porta, 2019).

Tics can be triggered by stressors (Lees, Robertson, Trimble, & Murray, 1984; Bornstein, Stefl, & Hammond, 1990; Robertson, Banerjee, Eapen, & Hixley, 2001; Caurín, Serrano, Fernández-Alvarez, Campistol, & Pérez-Dueñas, 2014) and by positive or negative emotional states, such as anxiety (Lees et al., 1984; Bornstein et al., 1990; Silva, Munoz, Barickman, & Friedhoff, 1995), repressed anger (Shapiro, Shapiro, Young, & Feinberg, 1988), euphoria, boredom, or fatigue. Some studies also identified factors leading to the reduction of tics, which include relaxation and concentration (Silva et al., 1995; Robertson et al., 2001; Eapen, Fox-Hixley, Banerjee, & Robertson, 2004; Caurín et al., 2014). Based on these grounds, the present study involved two activities, which can induce relaxation and concentration, and, therefore, bring to a possible improvement in TS symptoms: music-based motor activities and motor imagery activities.

1.1. Music-based motor activities

It has been demonstrated that the performance of specific voluntary movements can induce a tic reduction in people with TS (Thomalla, Jonas, Bäumer, Siebner, Biermann-Ruben, Ganos et al., 2014). More specifically, if voluntary motor activities involve the muscular districts affected by tics, a replacement of the tic with the voluntary gesture is possible, following the rationale of the Habit Reversal Training, i.e. a worldwide evidence-based therapy method addressed to TS patients (Azrin & Nunn, 1973; Woods, Piacentini, Chang, Deckersbach, Ginsburg, Peterson et al., 2008).

TS individuals show higher levels of creativity than neurotypical people (Zanaboni Dina, Leckman, & Porta, 2011; Espert, Gadea, Alino, & Oltra-Cucarella, 2017; Zanaboni Dina, Porta, Saleh, & Servello, 2017). Their creative skills can be channeled, together with their excessive motor energy, into different functional activities, promoting a decrease in tics while being
productive (Caurín et al., 2014). Within motor and creative activities, these patients should be addressed to opt for musical activities, because music induces them to perform fluid and rhythmic movements that contrast their tics (Bodeck, Lappe, & Evers, 2015; Scataglini, Andreoni, Fusca, & Porta, 2017). In fact, according to several studies (Zatorre, Halpern, Perry, Meyer, & Evans, 1996; Terry & Karageorghis, 2011), musical rhythm facilitates the coordination, by giving harmony to movements during a performance. More precisely, the temporal component of music leads the individual to follow the sequential structure and to “drag” movements.

The employment of music as a therapeutic tool has started to be explored over the last decades. Nowadays, many music-based methods are under investigation and they are applied in quite a wide range of disturbances, such as in the neurorehabilitation field (Bonacina, Cancer, Lanzi, Lorusso, & Antonietti, 2015; Cancer, Bonacina, Lorusso, Lanzi, & Antonietti, 2016; Cancer & Antonietti, 2017; Cancer, Stievano, Pace, Colombo, & Antonietti, 2019; Cancer, Bonacina, Salandi, Antonietti, Molteni, & Lorusso, 2020), but especially in cases of motor and speech disorders and emotional dysfunctions (Paul & Ramsey, 2000; Aldridge, 2005).

Music can be used in the rehabilitation aimed at reaching general goals (to motivate the patient, to induce a specific psychological state, to establish social relationships, etc.) or it can play a specific role. In the first case, music can be used to activate a psychophysiological state, an emotion, or to introduce interventions such as a psychotherapeutic session (Antonietti, 2009). For example, it has been found that music is a motivational input for elderly people in performing rehabilitation exercises and improving their quality of life (Sorrell & Sorrell, 2008). Music is also a tool to develop interpersonal contacts (Magee & Bowen, 2008): while listening to music, singing, or playing an instrument in group, people express feelings and thoughts that they could not be able to perform or verbalize without music. Music can trigger specific behaviors or cognitive processes that need to be rehabilitated (DeNora, 2000). This can be achieved with music accompanying motor/speaking tasks or it can be the exclusive rehabilitation task in itself (Antonietti, 2009; Antonietti, Colombo, & DeRocher, 2018). In this respect Särkämö and colleagues (2008) noticed that patients in post-stroke recovery who listened to music on a daily basis had more positive cognitive outcomes than patients who listened to audiobooks. Music was employed by Gervin (1991) in a study conducted on patients with motor disorders, who were affected by brain damage and, therefore, were characterized by an impairment in the areas of initiation, sequencing, and
motor planning; music was thus shown to encourage the synchrony between sounds and the patients’ gestures during a training session of getting dressed by themselves. Concerning tics, many patients reported a total absence of symptoms while being involved in a music task, such as playing an instrument, singing, or performing a musical piece, especially when the music task was active (e.g., playing guitar) rather than when it was a passive one (e.g., listening to music) (Lees et al., 1984; Sacks, 1995, 1998; Roessner, Banaschewski, & Rothenberger, 2004; Sacks, 2006, 2007; Robertson & Cavanna, 2008; Devlin, Alshaikh, & Pantelyat, 2019).

Besides motor activities, mood is another psychological state (see above, current subparagraph) that can also benefit from activities based on music (Lundqvist, Carlsson, Hilmersson, & Juslin, 2009; Schäfer, Sedlmeier, Stadtler, & Huron, 2013), which, in turn, can help to reduce tics when considering TS people. In the same way, the level of pleasure experienced by patients for a certain music piece (Bodeck et al., 2015) and for the type of task proposed with music (e.g., dancing) impacts on the mood (Groarke & Hogan, 2019) and, consequently, on the severity of tics when considering TS patients. In agreement with these findings, in the present study the choice of music and of the motor tasks were modulated by considering the possible effects on patients’ tics and on mood.

1.2. Motor imagery activities

Evidence in the literature (Jackson, Lafleur, Malouin, Richards, & Doyon, 2001; Sharma, Pomeroy, & Baron, 2006) has also suggested that the practice of motor imagery, in the absence of the actual execution of the movement, also improves the motor performance in patients with movement disorders. The same brain structures are indeed activated both when a person performs an action and when the person imagines to perform it (Jeannerod, 2001; Johnson-Frey, 2004). For this reason, mental practice sessions induce neuromodulation, similar to what happens following physical training (Trobia, Gaggioli, & Antonietti, 2011).

On this basis, various motor imagery trainings for motor rehabilitation have been proposed. Page and co-workers (2001) compared the efficacy of a rehabilitation program, consisting of imaginative tasks and occupational therapy, with the efficacy of the occupational therapy alone. Patients were trained to motor imagery for 10 minutes three times a week after each therapy session, and twice a week at home, for a total period of six weeks. The imagination of movements (for example, the act of grabbing a cup)
improved motor performance in stroke patients. Moreover, Stevens and Stoykov (2003) confirmed the effectiveness of a motor imagery training in the rehabilitation of hemiparesis. They found an improvement in the movement of the paretic limb’s wrist (e.g., manipulating objects) of patients who were involved in a rehabilitation program.

Only a handful of studies have employed motor imagery in the treatment of TS patients to date, to the best of our knowledge. Zago and colleagues (2014) investigated counterfactual thinking in a group of 48 TS subjects, who were instructed to perform unusual motor actions; counterfactual thinking resulted to be similar to that of healthy controls. Bodeck and colleagues (2015) employed music imagery tasks to improve tics, although motor imagery tasks were never employed for this goal.

In the present study we thus decided to include a motor imagery task with the aim of testing whether it could amplify the effect of the motor task on tics during the course of the training. The motor imagery task was not a variable of the study and for this reason it was carried out by all the participants. Given these premises (subparagraph 1.1, and current subparagraph), a motor imagery, music-based intervention, called “Imagine, Tourette!”, was developed.

2. Aims and Hypothesis

The purpose of this pilot study was to test the effect of the “Imagine, Tourette!” intervention on tics and on mood in patients with TS. The training consisted in finalistic motor tasks (dancing), to be achieved with and without music, and in motor imagery tasks (on dancing). The hypothesis was that music could reduce the severity of tics and have an effect on patients’ mood to a greater extent than the performance of the finalistic motor task alone, without the employment of music. References to music were deliberately omitted in the name of the training in order not to reveal the hypothesis of the study to the participants.

The improvement of tics and of mood could be expressed during and/or after the training sessions (refer, for example, to the previous studies on the effectiveness of music-based and music imagery trainings on tics during the session and for the following 15 minutes after the end of each session).

If this training led to positive results in the experimental subjects, it could be applied also to other individuals: young patients with Tourette Syndrome or patients with other motor disorders, such as stereotypies or mild
Parkinson’s Disease. Not the least, the training was very simple in order to be administered also thanks to the online-based method (see Procedure). Actually the possibility to stay at home for patients with motor disabilities, with no caregiver who was asked to move to the trainer’s office, made the training more feasible and easy to conduct. Furthermore, given the current COVID-19 pandemic, it was possible to perform the training without incurring in any risk of contagion also during lockdowns.

3. Methods

3.1. Participants

Eight TS patients from five Italian regions (Lombardy, Tuscany, Piedmont, Trentino-Alto Adige, and Emilia Romagna) volunteered to take part in the study. Inclusion criteria were the following: age between 20 and 35 and diagnosis of TS by a neurologist specialized in dealing with TS. All patients had already been engaged in cognitive-behavioral psychotherapy (CBT), i.e., Habit Reversal Training that is the gold standard CBT method for TS patients, for at least 4 months. Four participants were under pharmacological treatment (antipsychotics and antidepressants) for their TS, whereas in the others the medications were discontinued prior to enrollment in the study because of their improvements. The recruited patients were 6 males and 2 females (TS is predominant in males of the population with a 3:1 ratio; Leckman & Cohen, 1999), within the age range required by the study (mean age = 25.13 years; SD = 4.52). All participants received written and oral information about the study and signed the informed consent before the beginning of the intervention.

3.2. Procedure

A pseudo-randomized, control group design was applied.

First, two well known songs were selected to be used in the sessions of the training, i.e. “Gioca Jouer” by Cecchetto (song no. 1) and “Testa-spalla” by Don Lurio (song no. 2). Researchers opted for two songs, instead of only one, to limit the possibility that the musical experience was not pleasant enough: in fact, if one of the two songs, because of past experiences or idiosyncratic reactions, elicited negative emotions, the other one was thought to bring to a positive mood in the participants (it is unlikely that two songs had negative personal connotations for a same subject). An ad hoc
questionnaire was administered to all participants to assess their level of satisfaction regarding the two songs. Songs that were known were selected to promote a better control of the music variable: in this way, participants could not feel new and unexpected emotions. Moreover, the songs were also chosen because they both included pronounced movements the listener was invited to perform (e.g., song no. 1 quotes “sciare!” [ski!], which is an exhortation to make the skiing gesture).

Participants were divided into an experimental group and a control group of 4 subjects each, matching gender ($\chi^2 = 0; p = 1$), medication intake (y/n: $\chi^2 = .53; p = .46$), and level of satisfaction for the songs ($\chi^2 = 1.14; p = .28$).

The participants were exposed to a battery of standardized tests (see Assessment below) before, during, and after the intervention by a psychologist with a specific expertise in TS.

The intervention consisted of eight 15-minute individual sessions, within a two-week period. Sessions were online-based, using lap tops equipped with cameras. Trainers video-called patients on the web. Both the trainers and the patients were alone in a quiet room of their office/home. Trainers were two experts in TS treatment. The experimental group took part in motor activities based on music, whereas the control group was involved in the same tasks without music. The experimental group was asked to 1) watch a music video, in which dancers performed the dance moves along with the song and 2) repeat the movements of the dancers while re-watching the video. Controls were asked to perform the same two-step task but in the absence of music. From session 3 on, participants performed the movements while watching the video, i.e., the first step (watching without dancing) was not proposed anymore. During the training sessions the two songs were alternated (“Gioca Jouer” in sessions 1, 3, 5, 7; “Testa-Spalla” in the other sessions) in order to limit the impact of the emotions on the results that could be linked to a specific song.

The entire dataset of 8 participants also completed the same daily 3-minute motor imagery homework task. The task consisted in rethinking, into a private room, about the dancing of the last session. In this task participants were guided by a written list of sentences (e.g., “Try to recall the way you were dancing in the last session!”).
3.3. Assessment

The following battery of tests was used:

- **An ad hoc pleasantness questionnaire** (3-point Likert scale) to assess patients’ baseline pleasure in listening to songs 1 and 2.

- **Yale Global Tic Severity Scale – YGTSS** (Leckman, Riddle, Hardin, Ort, Swartz, Stevenson *et al.*, 1989). It is the most widely used clinical scale for the assessment of tic severity. It comprises an objective subscale, i.e., the severity of tics, and a subjective subscale, i.e., social impairment. It is completed by referring to the symptoms experienced during the previous week. Motor and sound tics are rated separately on 5 dimensions (e.g., tics’ frequency, tics’ intensity). The scale yields an objective double score for motor tics (0-25) and sound tics (0-25) and a subjective unified score for both motor and sound tics (0-50). It is important to notice that the two parts contribute equally to the global score, as social impairment is as fundamental as tic severity. At the end of each session, patients were assessed through tic objective (0-50) and subjective (0-50) scores. YGTSS scores were similar in the two groups at baseline (objective YGTSS: \( t = .02; p = .85 \); subjective YGTSS: \( t = .08; p = .94 \)).

- **Beck Depression Inventory-Second edition** (BDI-II; Beck, Steer, & Brown, 1996) is a 21-item self-report depression inventory. Each item is rated on a 4-point Likert scale, ranging from 0 to 3, with 3 being the worst score when considering the severity of symptoms. Items refer to how respondents have been feeling throughout the previous 2 weeks (e.g., crying, self-efficacy, sleep disorders, etc.). The maximum total score is 63. According to the BDI-II manual, scores from 0 to 13 indicate the absence of depressive symptoms, whereas scores from 14 to 63 indicate depressive symptoms (14-19 = mild depressive symptoms, 20-29 = medium-severity depressive symptoms, 30-63 = severe depressive symptoms). The BDI-II was administered at baseline (\( t_0 \)), at the end of the 4th session (\( t_1 \)), and at the last session (\( t_2 \)). The BDI-II was administered less frequently than the YGTSS because it is assumed that in two weeks TS patients should show a lower variability on mood than on tics. BDI-II scores were similar in the two groups at baseline (\( t = .84; p = .43 \)).
4. Data analyses

Descriptive analyses of the YGTSS (objective and subjective scores) and BDI-II scores were first performed, considering patients as single cases. Each patient’s outcome was reported. Considering the YGTSS, session 1 and session 7 were compared in relation to song 1 and session 2 and session 8 were compared in relation to song 2 (because these sessions were the first and the final session in which song 1 and song 2 were employed, respectively). Considering the BDI-II, the comparison was made between session 1 (t₀) and session 8 (t₂). Finally, group comparisons were performed using non-parametric statistics (Mann–Whitney U test; Alpha = .05), due to the small sample size, for all outcome variables (i.e., objective YGTSS, subjective YGTSS, and BDI-II).

4.1. The descriptive analyses for single cases

The outcome of the experimental group (patients no. 1 to no. 4) is described below (refer to Fig. 1-3). The percentage of improvement in the YGTSS outcome was first presented for each patient, followed by the percentage of unvaried or worsening in the YGTSS outcome. Finally, the percentage of improvement/unvaried/worsening of the BDI-II was reported for each patient (Tab. 1).

4.1.1. Patient no. 1

The patient obtained an improvement of 14% and of 10% in the objective and subjective YGTSS scores, respectively, in relation to song 2. In contrast, the patient showed no variations in the subjective YGTSS score (0% of change) and even a worsening (-10%) in the objective YGTSS score in relation to song 1. In terms of mood, the patient positively passed from BDI-II mild depressive symptoms (t₀) to the absence of depressive symptoms (t₂) with an improvement of 40%.

4.1.2. Patient no. 2

Patient no. 2 improved by 20% in the subjective YGTSS score in both songs, while no difference was detected in the objective YGTSS score in both songs from the beginning to the end of the training session (0% of change). Mood also improved from the beginning to the end of the training (BDI-II improvement of 40%).
4.1.3. Patient no. 3

Patient no. 3 improved in both the objective YGTSS score (a tic reduction of 44% in song 1, and of 26% in song 2) and in the subjective YGTSS score (the impairment reduced of 36% in song 1 and of 38% in song 2). Moreover, the patient obtained an improvement of 21% from the beginning \((t_0)\) to the end of the training \((t_2)\).

4.1.4. Patient no. 4

Regarding the objective YGTSS score, patient no. 4 obtained an improvement of 6% in song 1 and of 4% in song 2. Concerning the subjective YGTSS score, the patient improved (8%) in song 2, whereas she worsened (-14%) in song 1. The patient’s mood decreased (-21%), unfortunately, within the same BDI-II clinical range.

Table 1 – Individual results

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Experimental group</th>
<th>Song 1-improvement objective YGTSS</th>
<th>Song 2-improvement objective YGTSS</th>
<th>Song 1-improvement subjective YGTSS</th>
<th>Song 2-improvement subjective YGTSS</th>
<th>Improvement BDI-II</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-10%</td>
<td>14%</td>
<td>0%</td>
<td>10%</td>
<td>0%</td>
<td>40%</td>
</tr>
<tr>
<td>2</td>
<td>0%</td>
<td>0%</td>
<td>20%</td>
<td>20%</td>
<td>10%</td>
<td>40%</td>
</tr>
<tr>
<td>3</td>
<td>44%</td>
<td>26%</td>
<td>36%</td>
<td>38%</td>
<td>8%</td>
<td>21%</td>
</tr>
<tr>
<td>4</td>
<td>6%</td>
<td>4%</td>
<td>-14%</td>
<td>8%</td>
<td>-14%</td>
<td>-21%</td>
</tr>
<tr>
<td>5</td>
<td>30%</td>
<td>10%</td>
<td>50%</td>
<td>10%</td>
<td>-16%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0%</td>
<td>0%</td>
<td>11%</td>
<td>0%</td>
<td>0%</td>
<td>25%</td>
</tr>
<tr>
<td>7</td>
<td>26%</td>
<td>-6%</td>
<td>10%</td>
<td>-10%</td>
<td>-140%</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>-2%</td>
<td>6%</td>
<td>2%</td>
<td>2%</td>
<td>57%</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1 – Experimental group’s objective YGTSS scores
The control group (patients no. 5 to no. 8) obtained the following results (see Fig. 4-6). Also in this case, the percentage of improvement in the YGTSS outcome was first presented for each patient, followed by the percentage of unvaried or worsening in the YGTSS outcome. Finally, the percentage of improvement/unvaried/worsening of the BDI-II was reported for each patient (Tab. 1).

4.1.5. Patient no. 5

The patient obtained an improvement of 10% in both the objective and subjective YGTSS scores in relation to song 2. The participant, instead, showed an improvement of 30% and of 50% in the objective and subjective
Tourette music training

YGTSS score, respectively, in relation to song 1. Concerning the BDI-II scores, the subject worsened (-16%), however, within the same BDI-II clinical range.

4.1.6. Patient no. 6

Regarding song 1, participant no. 6 improved (11%) in the subjective YGTSS score, whereas no improvement was observed regarding the objective YGTSS score. Regarding song 2, the patient scored the same objective and subjective YGTSS results at the beginning and at the end of the training (0% of change). There was an improvement of 25% in BDI-II scores when comparing the first session ($t_0$) with the last session ($t_2$).

4.1.7. Patient no. 7

This patient scored positive results in the YGTSS measure in relation to song 1 (an improvement of 26% and of 10% in the objective and subjective YGTSS score, respectively), whereas the YGTSS score worsened in relation to song 2 (-6% and -10% in the objective and subjective score, respectively). The patient also worsened in the BDI-II score (-140%).

4.1.8. Patient no. 8

Patient no. 8 showed an improvement of 6% in the objective YGTSS score in relation to song 2 and of 2% in the subjective YGTSS score in relation to both songs. The objective YGTSS score slightly worsened (-2%) in relation to song 1. The patient improved of 57% in BDI-II scores from $t_0$ to $t_2$.

Figure 4 – Control group’s objective YGTSS scores
4.2. **Group comparisons**

Song 2 produced a specific improvement in subjective YGTSS scores, which were significantly higher in the music group than in the control group with a large size effect \(U = 1.50; p = .04; d = .81\), but not in objective YGTSS scores for which group comparisons did not reach statistical significance \(U = 4.5; p = .19; d = .44\). On the other hand, song 1 did not produce any specific improvement, as was shown by the non-significant difference between music and non-music groups in the improvement of YGTSS scores in relation to song 1 (objective YGTSS: \(U = 7.5; p = .61; d = .06\); subjective YGTSS: \(U = 6.00; p = .75; d = .25\)). Finally, music was found to have little effect on the BDI-II scores \(U = 3.5; p = .12; d = .56\).
5. Discussion and Conclusions

Music is an important rehabilitation tool. As a matter of fact, in the neurorehabilitation field the range of patients who could benefit from music interventions is broad, especially in cases of motor deficits (including TS), speech disorders, and emotional dysfunctions. The therapeutic use of music can induce a psychophysiological state of well-being and can improve mood. Motor and motor imagery tasks are indicated in TS in order to improve symptoms. The results of the current study are in line with this rationale. When considering the two groups, our study showed that music had a significantly positive effect on the impairment of tics in song 2. Some of the patients belonging to the experimental group of the “Imagine, Tourette!” training program showed a better outcome than the controls in the YGTSS measures (both objective and subjective scores), thus supporting the concept that music can be beneficial in the rehabilitation of motor impairments. Also considering the mood, the majority of individual cases in the experimental group showed a better outcome than the controls. In particular, a participant of the experimental group moved from BDI-II mild depressive symptoms to the absence of depressive symptoms and two other patients of the same group exhibited a large improvement.

During the course of the study, some unexpected outcomes also emerged. Participants showed different reactions based on the difficulty they perceived in performing the motor acts concurrently to the two songs. This depended on the speed of the songs (song 2 was faster than song 1), even though the required level of motor coordination to perform the dance movements was basic, and therefore comparable between the two songs. Furthermore, in most patients the motor imagery task re-evoked mood sensations they had experienced during the dance. The participants referred that the more they experienced positive mood sensations during the task, the fewer difficulties they had to learn the movements, and vice versa. We argue that the level of difficulty perceived affected the mood of the patients and had a potential positive or negative impact on self-esteem, and possibly on tic as well, during the activity. This variable needs to be further explored in future studies. Another unexpected outcome also emerged following the patients’ comments. Participants reported that song 1 was more “fluid” and therefore it induced fewer tics than song 2, which was perceived as “jerky”. Future considerations are needed in the selection of songs’ rhythm. Actually, Devlin and colleagues (2019) found that a music tempo between 105 and 125 beats per minute, a duple time, a clear downbeat, a moderate pulse...
clarity, and minimal key modulations are more effective in patients with movement disorders.

Although this is a pilot study and further research should be promoted, the positive findings regarding music-based interventions as reported in the literature (Gervin, 1991; Sorrell & Sorrell, 2008; Cancer et al., 2016) together with the results of the training presented here should encourage clinicians to suggest music activities (e.g., dancing) as a good practice for their TS patients to be combined within psychotherapy. As a matter of fact, during psychotherapy it is difficult to lead a patient to start and maintain a hobby with the aim of contrasting depressive symptoms. Indeed, motor and musical hobbies are recommended for patients suffering from TS and/or depressive symptoms. In addition, since TS people are particularly creative, hobbies could also maximize their creative potential. Interestingly, regarding the creative potential, one of the participants of the present study decided to enroll in a painting course after the end of the “Imagine, Tourette!” intervention, whereas he had never showed any interest in a hobby over the last two years of psychotherapy. This was a remarkable success, which may, however, be extended to more subjects in upcoming research studies, if you also consider the limitations.

5.1. Limitations

This study has some limitations, which should be accounted for and due to which the generalization of the results should be cautious. First of all, the sample size was small and for this reason no parametric statistical analyses could be conducted. Further studies should lead to multicentric studies involving more TS patients, including samples of TS children. After having applied the training session, as described in this paper, to larger TS datasets, the research could be extended to patients affected by other motor disorders, such as patients suffering from stereotypies or mild Parkinson’s Disease.

Another limitation of the current study is that four of the patients were medicated while the others were not. In future investigations, the variability of results due to drug administration should be measured and accounted for.

In addition, motor imagery tasks were not considered as a variable. Future studies should test the possible role of motor imagery as a therapeutic resource itself, given also the advantages of its practicality. Actually, motor imagery by itself, as opposed to listening to music and dance, can be used in absence of other tools (such as a tape recorder) and in public spaces without provoking embarrassment (because the individual does not have to dance).
Given the results, song 1 needs to be modified or proposed to different individuals. More in general, a refinement of the selection of songs is requested: offering songs with the appropriate features (e.g., rhythm, speed, and “fluidity” of music) could facilitate positive emotions and the performance of the motor tasks, and, consequent, reduction of TS symptoms.

Finally, considering the small number of participants, two pieces of music may have created a bias because it could have determined a further differentiation of the sample response, even by reducing the effect of pleasantness.

Notwithstanding, taking these conclusions and limitations into consideration, music-based motor and imagery tasks conducted with TS people have shown promising results and future investigations in this research field should be promoted in order to assess the efficacy of such an approach in the treatment of TS symptoms.

References


Parenting self-efficacy mediates the effect of parental acceptance on the social-emotional abilities of children with special needs

Wirza F. Rahayu\(^1\) & Frieda M. Mangunsong\(^1\)

Abstract

Parents of children with special needs face challenges that can cause stress and reduce parenting self-efficacy. The parent-child relationship is one of the main influences on a child's social-emotional abilities. The aim of this study was to examine more in depth the effect of parental acceptance on the social-emotional abilities of children with special needs and investigate the mediating role of parenting self-efficacy. The participants were 291 parents of children with special needs from various regions in Indonesia. All the participants completed a questionnaire that assessed parental acceptance, parenting self-efficacy, and the social-emotional abilities of their children. The mediation model was tested using the Structural Equation Model. The result of this study shows that the relationship between parental acceptance and the social-emotional abilities of children with special needs is fully mediated by parenting self-efficacy.

Keywords: Children with special needs; Disability; Mediation; Social-emotional abilities; Parental acceptance; Parenting self-efficacy.

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Conflict of Interest: The authors report no conflicts of interest.
1. Introduction

The arrival of a new child is an unforgettable event and one that can influence the stability of the parents’ relationship and provide a source of pride and happiness (Kandel & Merrick, 2007). However, the presence of children also requires adjustment and can trigger stress for couples and parents (Peterson & Hawley, 1998; Peterson, 2005). The role of parenting is a constant challenge for couples, starting from the child’s birth through to development into adulthood (Gargiulo, 2012). For parents of children with special needs, there are additional challenges and stress associated with childbirth and childrearing (Peterson, 2005). Parents who have children with special needs are often faced with various challenges in daily activities, due to developmental delays, limitations, or inabilities (Kubicek, Riley, Coleman, & Linder, 2013). Mangunsong (2014) defines children with special needs as children whose abilities deviate from the normal range for their age, including mental, sensory, physical, social, emotional, and communication abilities, as well as a combination of two or more of these aspects. Pratiwi and Mangunsong (2017) grouped children with special needs into three broad groups, namely children with physical barriers (e.g., limited mobility, visual impairment, and hearing damage), emotional and behavioral disorders (e.g., Attention-Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder, and learning disorders), and intellectual disability (e.g., Down Syndrome). In addition to deviations below normal, gifted children who have very high intelligence are also classified as children with special needs. The severity of a child’s disability affects various aspects of its development, including social-emotional abilities (Shonkoff, Hauser-Cram, Krauss, & Upshur, 1992).

The parents of children with special needs often feel a lack of self esteem, sadness, grief, and guilt, as well as difficulty in accepting their child’s disability, which can place them at a greater risk for other negative psychological conditions (Kubicek et al., 2013). Parents’ stress levels can affect their child's psychological well-being, while the child’s own stress, as a response to the parents’ limitations, can negatively affect cognitive, behavioral, and social-emotional development (National Scientific Council on the Developing Child, 2004). Research has described the social-emotional problems faced by children with special needs, including a preliminary study conducted by Diahwati, Hariyono and Hanurawan (2016) that showed that students with ADHD tend to exhibit deviant behavior and often get complaints from other students about disturbing behavior. Another
Parenting self-efficacy, parental acceptance and social-emotional abilities in special needs

study by Salimi, Mohammadi and Sadeghi (2016) found that children with visual impairment have lower emotional control abilities compared to children with normal vision, because children with visual impairments have difficulty in showing their proper emotional expression as a result of their limited vision.

Bagdi and Vacca (2005) emphasized that the foundation of children’s social and emotional development is embedded in positive emotional experiences between parents and children. This relationship forms the basis of how children see themselves, their friends, and the world around them. From the perspective of social learning, the relationship between children and parents is the main influence that shapes children's early social, emotional, and behavioral development, as well as influencing subsequent social-emotional abilities (Clark, Tluczek, & Cranley Gallagher, 2004; Powell & Dunlap, 2010). Scarupa (2014) defines social-emotional abilities as a broad set of abilities that can be taught and learned by children, which help them to manage emotions and behaviors effectively, be persistent in achieving their goals, appreciate learning processes, interact and work together effectively, and feel confident that they can achieve academically. Social-emotional abilities include various components, namely self-control, persistence, mastery orientation, academic self-efficacy, and social competence (Scarupa, 2014). The development of social-emotional abilities is believed to enable children to monitor themselves, their behavior, and interactions with the environment (Wilson, Gottfredson, & Najaka, 2001; Zins, Weissberg, Wang, & Walberg, 2004).

Saarni (1999) identified various skills acquired during the development of social-emotional abilities, including awareness of one's emotional state, ability to distinguish other people's emotional states, ability to use emotional words, empathy for others, and ability to deal with emotionally difficult situations. The ability to understand emotions becomes the foundation for developing social and emotional abilities. These various skills can certainly be achieved by children with special needs if their parents fully accept the limitations of their condition and provide continuous support to them (Hastings & Brown, 2002). Quality interaction with parents is critical for the healthy development of children’s social-emotional abilities (Brophy-Herb, Horodynski, Dupuis, Bocknek, Schiffman, Onaga, et al., 2009; Powell & Dunlap, 2010). By interacting with their parents, children also learn how to understand and regulate their emotions or behavior (Raikes, Robinson, Bradley, Raikes, & Ayoub, 2007). Social-emotional abilities are also the foundation for the development of cognition, language, and adaptability and
influence how children with special needs overcome daily challenges consistent with their developmental stage (Case-Smith, 2013). Children with special needs require psychological adjustment in the development of their social-emotional abilities, which is significantly influenced by parental acceptance of their condition (Rohner, 2014).

Parental acceptance is an active, conscious process that parents go through to understand the condition of their child’s special needs, which manifests in warmth, affection, attention, care, and support expressed both physically and verbally (Gargiulo, 2012). Rohner, Khaleque and Cournoyer (2012) define parental acceptance as a dimension of parental warmth in the process of childcare in the form of quality affection between parents and children. Parental acceptance has a significant influence on the adjustments in children with special needs, besides that parent acceptance also becomes the foundation related to how they jointly provide support and assist the development of the social-emotional abilities of children with special needs (Rohner, 2014). Research shows that parenting accompanied by warmth, responsibility, and positive expression contributes positively to the development of children's social-emotional abilities (Yagmurlu & Yavuz, 2015). A study by Izzo, Weiss, Shanahan and Rodriguez-Brown (2008) showed that parenting patterns marked by warmth and acceptance positively influence children's social-emotional adjustment. In Indonesia, the research conducted by Zahroh (2018) also showed that children with an impaired vision or hearing, impaired mobility, or mental disorders were more likely to have good social-emotional development if their parents demonstrated acceptance, affection, and emotional warmth.

Pozo and Sarria (2014) found that in the process of adjustment and acceptance of a child’s special needs, several things contribute to the mental health of parents, such as self-esteem and parenting self-efficacy. In support of these findings, several studies have also mentioned that a family environment characterized by interpersonal acceptance, where parents and children can accept each other, helps reduce the negative impact of the condition of the child’s special needs and reduces the emotional stress of parents. This can increase parents' confidence in their own parenting ability, commonly called parenting self-efficacy (Fernandes, Machado, & Machado, 2015). Conversely, failure in the process of accepting and identifying a child’s early social-emotional problems can negatively influence parenting self-efficacy, which can cause more serious problems for the child later in life (Carter, Briggs-Gowan, & Ornstein Davis, 2004). Moreover, Rohner and Khaleque (2008) state that the behavior of parents in childcare varies; such
is the difficulty of some parents in accepting their child’s social-emotional problems that they accept them only when they reject the limitations behind their child’s special needs. Acceptance and rejection of the condition of children's limitations are generally influenced by social and cultural factors, one of which is the environment in which there is a reciprocal relationship between parents and children. This is related to parenting practices and influences parenting self-efficacy.

Parenting self-efficacy is a parent’s belief or self-assessment, which consists in organizing and carrying out a set of tasks that are positively related to their child’s behavior and development (Coleman & Karraker, 2000). Parenting self-efficacy includes parents’ perception about their ability to deal with tasks related to abnormal development, certain diseases, or special needs of children. According to Coleman and Karraker (2000), there are five domains in parenting self-efficacy: 1) teaching discipline, 2) facilitating children's achievement in school (achievement), 3) supporting the child's need for recreation, 4) providing the child's emotional development (nurturance), and 5) maintaining the child's physical health. Parents with high parenting self-efficacy have higher interest, commitment, and persistence in parenting, and they are able to tolerate the challenges that arise and deal with the causes of stress effectively (Coleman & Karraker, 2005). Moreover, Junttila, Vauras and Laakkonen (2007) found that parenting self-efficacy has a positive relationship with the social abilities in children with special needs. Parenting self-efficacy has a major influence on the parent-child relationship, suggesting that increasing parenting self-efficacy is important for healthy child development. It is also positively related to parental acceptance and warmth in care-giving, consistent disciplinary practices, and children’s social development (Izzo et al., 2008).

The interrelationship of the three research variables (i.e. parenting self-efficacy, parental acceptance and children’s social-emotional abilities, see model below), is clear from the findings of previous studies, such as the work of Izzo and colleagues (2008), who described that parenting patterns marked by warmth and acceptance influenced children’s social-emotional adjustment more effectively. This research also supports the idea that increasing parenting self-efficacy in parenting practices is very important. In other words, parenting self-efficacy is an aspect that has a major influence on the role of parents as the closest person to the child in the care process. According to Izzo and collaborators (2008) parenting self-efficacy is related to the warmth in parenting, consistent disciplinary practices, and to the social-emotional development of children. The studies described above have
shown that both parental acceptance and parenting self-efficacy affect the social-emotional abilities of children with special needs and parental acceptance has a positive effect on parenting self-efficacy. Helping parents of children with special needs to understand and accept their child’s limitations is necessary to support both the well-being and confidence of parents and the social-emotional development of children (Mash & Wolfe, 2009). Based on the description above, it is known that the parental acceptance variable can influence the social-emotional abilities of children with special needs as well as influence parenting self-efficacy. The parenting self-efficacy variable can, in turn, also affect the social-emotional abilities of children with special needs. Thus, researchers suspect that the parenting self-efficacy variable can act as a mediator between parental acceptance and the social-emotional abilities of children with special needs. In addition, parenting self-efficacy also has an important mediational role in linking parents' personal factors, children's behavior, and situational factors, e.g., parenting self-efficacy can act as a mediator between parental loneliness and the social and academic abilities of children in schools (Junttila, Aromaa, Rautava, Piha & Raiha, 2015). However, no research has been conducted, to the best of our knowledge, on the mediating role of parenting self-efficacy between parental acceptance and social-emotional abilities of children with special needs. Whereas from previous research results it appears clear that parenting self-efficacy has an important role for the development of children with special needs. In an effort to compliment previous research, the present study investigated whether parenting self-efficacy acts as a mediator between parental acceptance and the social-emotional abilities of children with special needs.

The relationship between these three variables can be described as showed in Figure 1.

Figure 1 – The model of the relationship between research variables

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Parenting Self-Efficacy

Parental Acceptance  Social-Emotional Ability
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216
The model above can be tested because there is a link between the variable parental acceptance and the variable social-emotional abilities of children with special needs. The model also foresees a mediation variable that might influence the relationship between the two, namely parenting self-efficacy. The model, called mediation model, refers to the principle proposed by Baron and Kenny (1986) that a variable may be called a mediator if it influences the relationship between the independent variable (IV) and the dependent variable (DV). The mediation model, which is applied in this study, is based on the hypothesis that the IV affects the mediator variable, which, in turn, affects the DV. When the effect of the IV on the DV becomes insignificant in the presence of a mediator, full mediation occurs. The moderation model, instead, is based on the hypothesis that the moderating variable plays a role in strengthening or weakening the relationship between the independent variable and the dependent variable.

Research on children with special needs in Indonesia tends to focus more on enhancing the learning strategies and on developing academic abilities than on social-emotional development and studies typically target teachers or educators. For example, the use of multisensory methods to improve the recognition of number concepts for children with autism (Marienzi, 2012) and the evaluation of the learning abilities of children with special needs in inclusive classes (Maftuhatin, 2014) have been recent areas of inquiry for Indonesian researchers. Instead, parents’ role, as children’s closest caregivers, in the growth and development of children’s social-emotional development has often been overlooked. However, it is an important area for research because the social-emotional abilities of children with special needs has a life-long impact on their capacity to meet environmental demands, face various challenges, and achieve independence in daily life (Case-Smith, 2013). Although children can have multiple disability types, this study focuses on children with a single type of disability: either physical (limited mobility, vision and hearing impairment) or non-physical (such as ADHD and other learning difficulties and mild intellectual disability).

2. Aims and Hypotheses

2.1. Aims

The aims of this study were to investigate the effect of parental acceptance on the social-emotional abilities of children with special needs and to test whether parenting self-efficacy mediated this relationship.
2.2. Hypotheses

The present study tested one primary hypothesis followed by three subordinate hypotheses:

Primary Hypothesis: The relationship between parental acceptance and the social-emotional abilities of children with special needs is fully mediated by parenting self-efficacy. We predicted that the relationship between parental acceptance and social-emotional abilities would no longer be significant by adding parenting self-efficacy to the model tested in the primary hypothesis.

- Hypothesis a: Parental acceptance has a significant positive influence on the social-emotional abilities of children with special needs.
- Hypothesis b: Parental acceptance has a significant positive influence on parenting self-efficacy.
- Hypothesis c: Parenting self-efficacy has a significant positive influence on the social-emotional abilities of children with special needs.

3. Materials and Methods

3.1. Participants

The participants in this study were 291 parents of children with special needs with two types of disabilities: physical disabilities and non-physical disabilities (mental and behavioral disorders). Physical disabilities thus included motor movement disorders, visual impairment and hearing loss, while non-physical disabilities, or mental and behavioral disorders, included mild intellectual disability, ADHD, specific learning disorders (dyslexia, dysgraphia, and dyscalculia), excluding the autistic spectrum disorder, cerebral palsy, Down syndrome, or double handicap. The children were attending elementary school or its equivalent. All participants lived in Indonesia and spoke Indonesian fluently. Participants were mostly (86.9%) females and the mothers of the children with special needs, while the fathers figured in only 13.1% of cases. The average age of the mothers was 40 years old (range = 25 to 56 years) while that of the fathers was 42 years old (range = 20 to 65 years). Most participants had finished high school. The participants’ children with special needs were more boys than girls, and more children with non-physical disabilities, such as mild intellectual disability and ADHD. Most of the children were in grades 1 to 3. The children were aged between 5 to 16 years old. To recruit participants, we
approached educational and community organizations catering to families with children with special needs, such as public and private elementary schools, special needs schools, special needs observers, and communities of parents of children with special needs. We approached all institutions both by visiting in person and by telephone. After obtaining permission, we produced a research permit and informed consent and immediately conducted the research by distributing written questionnaires to the participants. In addition, questionnaires were also distributed online. After completing the questionnaire that was delivered, each participant obtained a reward in the form of electrical pulses (for online participants), which were sent via the go-pulse feature on the Go-jek application (one of the online start-up applications in Indonesia). To offline participants we gave gift bags as reward. The sample in this study was obtained by convenience sampling, subject to the availability and willingness of participants who met the research criteria (Cohen, Swerdlik, & Phillips, 2009; Creswell & Clark, 2017).

3.2. Instruments

3.2.1. Social-emotional ability

Social-emotional ability was measured using a modified version of an instrument designed to assess the social-emotional skills of elementary students, compiled by Child Trends and the Tauck Family Foundation-Teacher Survey (Scarupa, 2014). After the adaptation process to the Indonesian version, the test tool was called Elementary Student's Social-Emotional Skills Measurement. This instrument was divided into two parts: 1) a teacher survey, covering self-control, persistence, and social competence, and 2) a student survey covering self-control, persistence, mastery orientation, and academic self-efficacy. According to Scarupa (2014), student surveys can only be administered to high school elementary students (grades 3-5, aged 8 to 11 years) because they are predicted to be able to provide appropriate answers. In contrast, lower class students are still considered not able to understand the concept of self-ability and mastery orientation based on their developmental stage. Based on the explanation above, we decided to use the items in the teacher survey to measure the child's social-emotional abilities and the components that were used were thus persistence, self-control and social competence.

Elementary Student's Social Emotional Skills Measurement was developed by Scarupa (2014) to measure children's social-emotional abilities
Life Span and Disability

Rahayu W. F. & Mangunsong F. M.

in school settings related to academic achievement. However, he explained that the measuring instrument can be adapted to other contexts that target social-emotional abilities. Thus, the teacher survey-measuring instrument in this study was adapted to the research context and administered to parents having children with special needs. This measurement tool covers three dimensions of social-emotional abilities: persistence, self-control, and social competence. The original version of this measurement tool consists of 12 items with responses rated on a four-point Likert scale (1 = "never" to 4 = "always").

This measurement tool is not available yet in Indonesian, so we translated the items from English to Indonesian. We also adapted it by adding a further nine items to make it more relevant to parents of children with special needs.

Table 1 – The latest version of the Elementary Student's Social-Emotional Skills Measurement tool that was adapted to the Indonesian version

<table>
<thead>
<tr>
<th>No</th>
<th>Statement</th>
<th>N</th>
<th>ST</th>
<th>O</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>When given an assignment/asked to do something, my child does it thoroughly.</td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td>My child gives up easily when he/she performs a difficult task.</td>
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<tr>
<td>3</td>
<td>My child makes no effort to get what he/she wants.</td>
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<tr>
<td>4</td>
<td>My child tends to move on to other tasks before completing the first task.</td>
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<tr>
<td>5</td>
<td>My child is able to wait his/her turn patiently/queue.</td>
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<tr>
<td>6</td>
<td>My child can sit still in situations that require him/her to sit still.</td>
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<tr>
<td>7</td>
<td>If his/her wish is not fulfilled, my child can go berserk.</td>
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<tr>
<td>8</td>
<td>My child interferes with other people's ongoing activities that trigger conflict.</td>
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<tr>
<td>9</td>
<td>While working on assignments, my child refuses to correct mistakes.</td>
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<tr>
<td>10</td>
<td>My child can do routine tasks without being reminded.</td>
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<tr>
<td>11</td>
<td>My child can do activities in a group.</td>
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<td></td>
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<tr>
<td>12</td>
<td>My child can solve problems with peers/groups without acting aggressively.</td>
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<tr>
<td>13</td>
<td>My child is willing to share with others.</td>
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<tr>
<td>14</td>
<td>My child can take the initiative to invite friends to do activities in the group.</td>
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<tr>
<td>15</td>
<td>My child can show expressions appropriate to the circumstances experienced by other people.</td>
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<tr>
<td>16</td>
<td>My child is neglected by friends in group activities for insisting on his/her will.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>When conflicted with peers/groups, my child can solve his/her problems.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>After completing the assignment, my son/daughter rechecks the results.</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>19</td>
<td>My child refuses to play in groups.</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Abbreviations: N = Never; O = Often; ST = Sometimes; A = Always.

A readability test was performed on individuals who met the research characteristics. Furthermore, we conducted analyses to test the validity and reliability of this instrument. As a result, two items were invalidated and, therefore, eliminated, resulting in 19 items used in the final version (see Tab. 1). The results of a confirmatory factor analysis (CFA) on these 19 items supported their validity: \( \chi^2 (149) = 1.224, p \leq .0001, CFI = .847, RMSEA = \ldots \)
Parenting self-efficacy, parental acceptance and social-emotional abilities in special needs

0.071 [90% CI 0.060, 0.079], SRMR = 0.075. Factor loadings of the items ranged from 0.466 to 0.737. The Cronbach’s alpha of this measuring instrument was 0.872 and the correlation between items with the total score ranged from 0.331 to 0.612.

3.2.2. Parental acceptance

Parental acceptance was measured using the Parental Acceptance-Rejection Questionnaire Short Form (PARQ-SF) developed by Rohner, Khaleque and David (2005). This measurement tool measures the level of parental acceptance perceived by parents towards their children. The choice of answers is again in the form of a Likert scale in the range 1-4, where "1" means "very incompatible" and "4" means "very compatible". This measurement was adapted into Indonesian by Fath (2015), which consists of 16 items and is given to parents of children with autism. This measurement tool is used for trials, after which an adaptation and readability test is carried out to suit the criteria of the given participants. We adjusted this instrument for parents of children with special needs and conducted readability tests with the 291 participants. Based on the results of testing the instrument and item analysis, 15 items were considered valid and reliable and were included in this study (see Tab. 2). The 1 invalid item (i.e. "I really care about the difficulties of my child") presented a correlation between items and a total score below 0.3.

Table 2 – The latest version of the Parental Acceptance-Rejection Questionnaire Short Form (PARQ-SF) tool that was adapted to the Indonesian version

<table>
<thead>
<tr>
<th>No</th>
<th>Statement</th>
<th>VI</th>
<th>I</th>
<th>C</th>
<th>VC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I do not pay attention to my child as long as he/she doesn't bother me.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>I hit my son/daughter even though he/she didn’t deserve it.</td>
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<td></td>
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<tr>
<td>3</td>
<td>I care about what my child thinks and encourage him/her to talk about it.</td>
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<td></td>
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</tr>
<tr>
<td>4</td>
<td>I feel that other kids are better than mine in many ways.</td>
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<td></td>
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</tr>
<tr>
<td>5</td>
<td>I feel annoyed with my child.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>6</td>
<td>I make my child feel unloved if he/she is naughty.</td>
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<td></td>
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</tr>
<tr>
<td>7</td>
<td>I care about the hardships my child is facing.</td>
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</tr>
<tr>
<td>8</td>
<td>I ignored my son/daughter when he/she asked for help.</td>
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</tr>
<tr>
<td>9</td>
<td>I treat my child with gentle and loving care.</td>
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<td></td>
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</tr>
<tr>
<td>10</td>
<td>I tend to ignore my children.</td>
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</tr>
<tr>
<td>11</td>
<td>I hurt my child’s feelings.</td>
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<tr>
<td>12</td>
<td>I beat my child when I get angry.</td>
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<tr>
<td>13</td>
<td>I openly declare to my child that I love him/her.</td>
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<tr>
<td>14</td>
<td>I consider my child a burden of my life.</td>
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<tr>
<td>15</td>
<td>I give full attention to my child.</td>
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</tbody>
</table>

Abbreviations: VI = Very Incompatible; C = Compatible; I = Incompatible; VC = Very Compatible
The CFA results for this instrument were $\chi^2 (90) = 1.527$, $p = .002$, CFI = .924, RMSEA = .041 [90% CI .028, .052], SRMR = .057. Factor loadings for the items ranged from .308 to .806. The Cronbach’s alpha of this instrument was .844 and the correlation between items and the total score ranged from .335 to .707.

3.2.3. Parenting self-efficacy

Parenting self-efficacy was measured using the Self-Efficacy for Parenting Task Index developed by Coleman and Karraker (2000), which was adapted for Indonesian by Madjid and Mayangsari (2011) from the parenting self-efficacy research group. This instrument consists of 36 items that measure five domains of parenting self-efficacy in parents who have children aged 5 to 12 years (Coleman & Karraker, 2000).

Table 3 – The latest version of the Self-Efficacy for Parenting Task Index tool that was adapted to the Indonesian version

<table>
<thead>
<tr>
<th>No</th>
<th>Statement</th>
<th>VI</th>
<th>I</th>
<th>C</th>
<th>VC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I am quite capable of guiding my child to obey the rules that I set.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2</td>
<td>I find it hard to make proper rules for my child.</td>
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</tr>
<tr>
<td>3</td>
<td>I find it hard to teach my children to obey my commands.</td>
<td></td>
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</tr>
<tr>
<td>4</td>
<td>Compared to teaching other things, I have more difficulty to discipline my children.</td>
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<tr>
<td>5</td>
<td>My efforts to teach discipline to my child are vain.</td>
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</tr>
<tr>
<td>6</td>
<td>I can discipline my child in many ways.</td>
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<tr>
<td>7</td>
<td>I can do the things that are needed when my child is doing his/her schoolwork.</td>
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<tr>
<td>8</td>
<td>I am involved in my child's school activities as much as possible.,</td>
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<td></td>
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<tr>
<td>9</td>
<td>Teaching my child to do schoolwork frustrates me.</td>
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<td></td>
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<tr>
<td>10</td>
<td>I find it hard to be involved in my child’s educational activities as I would like to do.</td>
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<td></td>
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</tr>
<tr>
<td>11</td>
<td>I can guide my child to solve his/her school problems.</td>
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<td></td>
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</tr>
<tr>
<td>12</td>
<td>I have done the necessary things when teaching my child to play with his/her friends.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>13</td>
<td>I feel inadequate to make my child happy.</td>
<td></td>
<td></td>
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<tr>
<td>14</td>
<td>I feel satisfied that I can provide fun activities for children.</td>
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<tr>
<td>15</td>
<td>I care less about my child’s social life.</td>
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<tr>
<td>16</td>
<td>I can share joyful experiences with my children.</td>
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<tr>
<td>17</td>
<td>I do not engage in activities that are fun for children.</td>
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<tr>
<td>18</td>
<td>I am a loving and caring parent for my child.</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>19</td>
<td>I find it hard to show my love for my child.</td>
<td></td>
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<tr>
<td>20</td>
<td>I feel that I have provided support in every activity of my child following his/her expectations.</td>
<td></td>
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<tr>
<td>21</td>
<td>It’s easy for me to be a loving parent.</td>
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<td></td>
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<tr>
<td>22</td>
<td>I encourage my child to show his/her feelings.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>I have done everything that is necessary to make my child healthy.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Being busy makes it difficult for me to pay attention to my child’s health.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>I can make sure that my child feels that his/her health is being monitored.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: VI = Very Incompatible; C = Compatible; I = Incompatible; VC = Very Compatible;
The choice of answers is again in the form of a Likert scale in the range 1-4, where "1" means "very incompatible" and "4" means "very compatible". The Cronbach Alpha coefficient of this measuring instrument is .918. Although this measurement was adapted into Indonesian by Wardani (2013), we decided to revise these items in accordance with the context and participants of our dataset. Based on the results of testing the measuring instrument and item analysis, 25 items were considered valid and reliable and were included in this study (refer to Tab. 3). The CFA results for this instrument were $\chi^2 (275) = 1.502, p \leq .0001$, CFI = .801, RMSEA = .066 [90% CI .060, .071], SRMR = .076. Factor loadings for the items ranged from .308 to 806. The Cronbach’s alpha of this instrument was .906 with the correlation between items and the total score in the range .418 to .610.

3.3. Procedure

The study was conducted from May to September 2019. The several measuring instruments were put together in a single questionnaire document. After obtaining a research ethical clearance and permit, we visited several special schools in the Greater Jakarta Area, organizations and therapy sites to obtain participants offline. The process of filling out the questionnaire was carried out directly on the day of the encounter with the participants and we collected all the questionnaires that had been filled out. To make it more practical and smooth for the participants, we created an online version of the questionnaire and gave participants the choice of completing the questionnaire via a link online or in paper format. Of the 291 participants who completed the questionnaire, 57.7% filled out the paper version and 42.3% completed it online. Prior to starting the questionnaire, we conveyed the general purpose of the research to all the participants and each was asked to give his/her informed consent by signing in writing on the questionnaire form as proof that the research adhered to ethical standards.

3.4. Data processing and analytical strategy

Data processing and analyses were performed using IBM SPSS Statistics for Windows (version 22) and R studio (version 1.1.383) with Lavaan 0.6-5. Cronbach’s $\alpha$ and corrected item-total correlations were used to test the validity and reliability of the measuring instruments. Descriptive statistics were computed to provide an overview of parents’ and children’s demographic characteristics through percentage, frequency, mean, standard
deviation, and minimum and maximum values, related to both demographic conditions and each variable. Furthermore, to test the fitness of the theoretical model and examine the role of parenting self-efficacy in mediating the effect of parental acceptance on the social-emotional abilities of children with special needs, the Structural Equation Model in R studio program was used. Statistical significance was set at $p < .05$.

According to Hu and Bentler (1998), a SEM is said to be a good fit to the observed data if the Comparative Fit Index (CFI) is between .90 and .95, the value of the Root Mean Squared Error of Approximation (RMSEA) is less than .06, and the Standardized Root Mean Square Residual (SRMR) is less than .08. Browne and Cudeck (1993) state that RMSEA numbers less than .05 indicate a good model fit, and RMSEA values between .05 to .08 indicate that the model is still acceptable. Hu and Bentler (1998) state that a model is said to fit the data if it meets at least two of the indicators mentioned above.

4. Data Analysis

4.1. Results

Table 4 shows participants’ parental roles, age, and education level. The average age of female participants was 40 years old (range = 25 to 56 years old), while the average age of male participants was 42 years old (range = 20 to 65 years old). As results from the table, most participants had finished high school.

Table 4 – The characteristics of the participants ($n = 291$)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Categories</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenting role</td>
<td>Father</td>
<td>38</td>
<td>13.1%</td>
</tr>
<tr>
<td></td>
<td>Mother</td>
<td>253</td>
<td>86.9%</td>
</tr>
<tr>
<td>Father’s age</td>
<td>Young adult (20-39 years old)</td>
<td>10</td>
<td>3.4%</td>
</tr>
<tr>
<td></td>
<td>Middle adulthood (40-65 years old)</td>
<td>27</td>
<td>9.3%</td>
</tr>
<tr>
<td></td>
<td>Not identified</td>
<td>1</td>
<td>.3%</td>
</tr>
<tr>
<td>Mother’s age</td>
<td>Young adult (25-39 years old)</td>
<td>124</td>
<td>43.0%</td>
</tr>
<tr>
<td></td>
<td>Middle adulthood (40-56 years old)</td>
<td>125</td>
<td>43.0%</td>
</tr>
<tr>
<td></td>
<td>Not identified</td>
<td>4</td>
<td>1.4%</td>
</tr>
</tbody>
</table>
Parenting self-efficacy, parental acceptance and social-emotional abilities in special needs

Table 5 shows the characteristics of the participants’ children with special needs. There were more boys than girls and more children with non-physical disabilities, such as mild intellectual disabilities and ADHD, than children with physical disabilities. Most of the children were in elementary school grades 1 to 3 and were aged between 5 and 16 years old (majority aged 8 to 13 years old), with the exception of one child who was over 16 years old.

Table 5 – The characteristics of the participants’ children with special needs (n = 291)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Categories</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Boys</td>
<td>165</td>
<td>56.7%</td>
</tr>
<tr>
<td></td>
<td>Girls</td>
<td>126</td>
<td>43.3%</td>
</tr>
<tr>
<td>Type of disability</td>
<td>Physical</td>
<td>135</td>
<td>46.4%</td>
</tr>
<tr>
<td></td>
<td>Non-physical</td>
<td>156</td>
<td>53.6%</td>
</tr>
<tr>
<td>Elementary school grade</td>
<td>1</td>
<td>96</td>
<td>33.0%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>44</td>
<td>15.1%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>53</td>
<td>18.2%</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>35</td>
<td>12.0%</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>37</td>
<td>12.7%</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>26</td>
<td>8.9%</td>
</tr>
</tbody>
</table>

Father’s education

| Primary School | 4 | 1.4% |
| Junior High School | 1 | 0.3% |
| Senior High School | 18 | 6.2% |
| Diploma | 2 | 0.7% |
| Undergraduate degree | 9 | 3.1% |
| Master’s degree | 3 | 1.0% |
| Doctoral degree | 1 | 0.3% |

Mother’s education

| Primary School | 9 | 3.1% |
| Junior High School | 39 | 13.4% |
| Senior High School | 110 | 38.1% |
| Diploma | 28 | 9.6% |
| Undergraduate degree | 54 | 18.6% |
| Master’s degree | 13 | 4.5% |
Table 6 shows an overview of the research variables based on the descriptive statistical calculations.

### Table 6 – Overview of the research variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Min Average</th>
<th>Max Average</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social-emotional abilities</td>
<td>1</td>
<td>4</td>
<td>2.67</td>
<td>.50</td>
</tr>
<tr>
<td>Parenting self-efficacy</td>
<td>1</td>
<td>4</td>
<td>2.58</td>
<td>10.32</td>
</tr>
<tr>
<td>Parental acceptance</td>
<td>1</td>
<td>4</td>
<td>3.51</td>
<td>.64</td>
</tr>
</tbody>
</table>

Scores of the three measuring instruments were grouped into three categories: low (1-1.99), moderate/adequate (2-3), and high (3.01-4) with a range of answers 1-4 on the Likert scale. The minimum value obtained from the lowest weight multiplied by the number of items, while the maximum value obtained from the highest weight multiplied by the number of items. In addition, the average score obtained from the lowest weight multiplied by 2. Concerning the social-emotional and the parenting self-efficacy variables, the mean was 2.67 and 2.58, respectively. This shows that the average parent's assessment of the social-emotional abilities of children with special needs and the level of parenting self-efficacy of the participants were both moderate. The parental acceptance variable showed, instead, that the level of acceptance was high with a mean of 3.51. This shows that the average parent shows a high acceptance of the condition of their children with special needs.

To test the fitness of the theoretical model and examine the role of parenting self-efficacy in mediating the effect of parental acceptance on the social-emotional abilities of children with special needs, we conducted a mediation test, treating parental acceptance as the independent variable, parenting self-efficacy as the mediator, and social-emotional abilities of children with special needs as the dependent variable. Table 7 shows the fit indices for each model and also the regression coefficients (B), standardized regression coefficients (β), and statistical significance (p-values). Based on the primary hypothesis and on the model fit criteria proposed by Hu and Bentler (1998) and Browne and Cudeck (1993), the mediation model tested...
in this study was an acceptable fit to the observed data and the model was further analyzed (refer to Tab. 8 for details). The regression of parental acceptance (X) on the social-emotional abilities (Y) was significant ($p < .005$). The regression of parental acceptance (X) on parenting self-efficacy (M) was also significant ($p < .005$) as well as that of parenting self-efficacy (M) on the social-emotional abilities (Y) ($p < .005$).

Table 7 – Fit indices for each model (n = 291)

<table>
<thead>
<tr>
<th>Model</th>
<th>CFI</th>
<th>RMSEA</th>
<th>SRMR</th>
<th>Sig.</th>
<th>B</th>
<th>β</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Parental acceptance (X) to social-emotional abilities (Y) through parenting self-efficacy (M)</td>
<td>.766*</td>
<td>.047*</td>
<td>.078*</td>
<td>.000*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>a. Parental acceptance (X) to social-emotional abilities (Y)</td>
<td>.844</td>
<td>.048</td>
<td>.070</td>
<td>.000*</td>
<td>.338</td>
<td>.260</td>
</tr>
<tr>
<td>b. Parental acceptance (X) to parenting self-efficacy (M)</td>
<td>.776*</td>
<td>.052*</td>
<td>.078*</td>
<td>.000*</td>
<td>.589</td>
<td>.646</td>
</tr>
<tr>
<td>c. Parenting self-efficacy (M) to social-emotional abilities (Y)</td>
<td>.790*</td>
<td>.054*</td>
<td>.076*</td>
<td>.000*</td>
<td>.431</td>
<td>.312</td>
</tr>
</tbody>
</table>

Abbreviations: X = independent variable; Y = dependent variable; M = mediator. CFI = Comparative Fit Index; RMSEA = Root Mean Squared Error of Approximation; SRMR = Standardized Root Mean Square Residual. * indicates that the model fit indices were acceptable, according to Hu and Bentler (1998).

Table 8 shows the regression coefficients (B), standardized regression coefficients (β), and statistical significance ($p$-values) for each of the models tested. The results support the mediation effect predicted in the primary hypothesis. When parenting self-efficacy was added to the model, the direct effect of parental acceptance (X) on the social-emotional abilities (Y) was not significant ($p = .271$). When the indirect effect of parental acceptance on the social-emotional abilities of children with special needs was mediated by the parenting self-efficacy variable, the results became significant ($p = .030$). In this model, parenting self-efficacy fully mediated the effect of parental acceptance on the social-emotional abilities of children with special needs. The regression of parental acceptance (X) on the social-emotional abilities (Y), ignoring parenting self-efficacy (M), was also significant ($p < .005$). Thus, the more parents accepted the limitations of their children’s condition, the better were the social-emotional abilities of their children. The regression of parental acceptance (X) on parenting self-efficacy (M) was also significant ($p < .005$). Parents who reported higher levels of acceptance tended to report higher levels of self-efficacy. Thus, the hypothesis that parenting self-efficacy (M) mediated over the control of parental acceptance
(X), significantly predicting the social-emotional abilities (Y) of children \( (p = .013) \), was supported. Higher self-efficacy among parents was associated with higher social-emotional abilities in their children.

Table 8 – *Mediation test results* \( (n = 291) \)

<table>
<thead>
<tr>
<th>Parenting self-efficacy (M)</th>
<th>Social-emotional abilities (Y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( B )</td>
<td>( \beta )</td>
</tr>
<tr>
<td>Direct effect</td>
<td></td>
</tr>
<tr>
<td>Parental acceptance (X)</td>
<td>( a )</td>
</tr>
<tr>
<td>Parenting self- efficacy (M)</td>
<td>-</td>
</tr>
<tr>
<td>Indirect effect</td>
<td>( ab )</td>
</tr>
<tr>
<td>Total effect</td>
<td>.340</td>
</tr>
</tbody>
</table>

Abbreviations: * indicates statistical significance at \( p < .05 \); \( c' \) represents the direct effect of X on Y after controlling for M. The effect of X on M is represented by \( a \), and the effect of M on Y, controlling for X, is represented by \( b \). The indirect effect is the product of \( a \) * \( b \).

Figure 2 illustrates the indirect effect of parental acceptance on the social-emotional abilities, mediated by parenting self-efficacy.

Figure 2 – *Final structural model with path coefficients depicting parenting self-efficacy as a mediator between parental acceptance and social-emotional abilities of children with special needs*

\[ a = .645* \]
\[ b = .243* \]
\[ c' = .103 \]

*Indirect effect = .157*  
*Total effect = .260*  

Notes: * indicates statistical significance at \( p < .05 \); \( c' \) represents the direct effect of X on Y after controlling for M. The effect of X on M is represented by \( a \), and the effect of M on Y, controlling for X, is represented by \( b \). The indirect effect is the product of \( a \) * \( b \).
5. Discussion

The findings highlighted in this paper indicate that parenting self-efficacy plays a significant role in mediating the effect of parental acceptance on the social-emotional abilities of children with special needs. This is consistent with Izzo and collaborators (2008) who found that a high degree of parenting self-efficacy plays a significant role in providing good care and warmth and affection for children so that it also has a good impact on children's development, including the child's social-emotional development.

Previous research has shown that when parents accept the limitations imposed by their children’s physical or non-physical disability, children develop stronger social-emotional abilities than if their parents do not accept their condition (Izzo et al., 2008; Rohner, 2014; Yagmurlu & Yavuz, 2015). In this study, we explored the mediating role of parenting self-efficacy in the effect of parental acceptance on the social-emotional abilities of children with special needs. In support of the primary hypothesis, we found that the effect of parental acceptance on the social-emotional abilities of children with special needs was significantly mediated by parenting self-efficacy. Parental acceptance influenced the development of the social-emotional abilities of children with special needs, via parenting self-efficacy. If parents of children with special needs fail to understand and accept the limitations of their child's condition, then this affects their confidence as a parent. Fernandes and co-workers (2015) stated that a family environment characterized by interpersonal acceptance in which parents and children can welcome each other will help reduce the negative impact of the condition of the limitations of children with special needs in order as to reduce the emotional stress of the parents to lower stress levels. This can then increase parents' confidence in their ability to care, commonly called parenting self-efficacy. This is in line with the findings of Briggs-Gowan and Carter (2007) who observed that the failure of parents to identify early social-emotional problems negatively affects parenting self-efficacy. Furthermore, parental acceptance of children with special needs affects the development of children's social-emotional abilities (Jones & Prinz, 2005). As mentioned above, Junttila and co-workers (2007) found that parenting self-efficacy has a positive relationship with social-emotional abilities in children with special needs.

When parenting self-efficacy was not controlled for, we found that parental acceptance positively influenced the social-emotional abilities of children with special needs. That is, the more parents can accept the
conditions or limitations that their children have, the better are the social-emotional abilities of their children. These results are in line with research by Zahroh (2018), which showed that children with impaired vision or hearing, impaired mobility, or a mental disorder were more likely to have good social-emotional development if their parents demonstrated acceptance, affection, and emotional warmth. This explains that the role of parental acceptance is important for the development of social-emotional abilities of children with special needs.

As predicted, it was found that parental acceptance had a significant positive association with parenting self-efficacy. Parents are not always able to accept the limitations of the conditions behind their child’s special needs. Most parents experience negative psychological states in response to their child’s condition, such as stress or denial. Hallahan, Kauffman and Pullen (2012) reported that parents who have children with special needs have a high probability of experiencing stress and stress-related problems. This manifests in emotional reactions, namely guilt, anger, and denial, until finally reaching acceptance. Thus, it appears that parental acceptance is a process in which individuals typically experience a range of psychological and emotional states before reaching the stage of acceptance. According to Kandel and Merrick’s (2007) review, parents who have children with special needs usually experience critical periods, in which a crisis needs to be resolved, although these are not the same for everyone. If parents manage to overcome these crises, they will reach the stage of acceptance. When parents accept their child with special needs, it is easier for them to feel confident in providing the best care as a parent. Kandel and Merrick (2007) stated that parents who accept their child’s special needs are more capable of caring for themselves and meeting the needs of their children.

Our research also showed that parenting self-efficacy had a significant positive effect on the social-emotional abilities of children with special needs. This is consistent with research conducted by Junttila and co-workers (2007). Thus, it appears that when parents feel confident in dealing with the conditions and limitations imposed by their child’s disability, this has a positive impact on the development of children's social and emotional abilities. Furthermore, other research conducted by the same authors (Junttila et al., 2015) showed that parenting self-efficacy was the main element in improving children's well-being and development in various aspects, including their social-emotional abilities. In line with these findings, Carter and collaborators (2004) stated that high parenting self-efficacy can
reduce stress and depression in parents with children with special needs and can help their children’s social-emotional development.

As mentioned above, the interrelationships of the three variables of this study have already been explained by Izzo and colleagues (2008), who stated that parental care accompanied by warmth and acceptance positively influences the child’s social-emotional adjustment. In addition, an increased parenting self-efficacy in parenting practices also has a positive impact on children's development. In other words, parenting self-efficacy is an aspect that has a significant influence on the role of parents as the closest person to the child in the caring process. Facing a situation like this requires a good ability from parents to be able and to be independent in taking care of children with special needs. These previous studies are thus consistent with our finding that parenting self-efficacy acts as a significant mediator in the influence of parental acceptance on the social-emotional abilities of children with special needs.

It should be underlined, however, that this study has several limitations. Previous research found that parents with young children with special needs showed a higher level of self-efficacy than parents with adolescent children with special needs (Glatz & Buchanan, 2015). In the study presented here, most participants had children who were aged under 13 years old. Therefore, our sample may not be representative of parents with older children with special needs. Future studies should replicate our model with parents of older children with special needs. Research has also found other socio-demographic variables that may influence parenting self-efficacy. For example, parents with low levels of education and income tend to have lower levels of parenting self-efficacy than parents with higher levels of education and income (Glatz & Buchanan, 2015). Likewise, low income is associated with increased symptoms of depression among parents, which results in decreased parenting self-efficacy (O’Neil, Wilson, Shaw, & Dishion, 2009). Furthermore, Juntila and co-workers (2015) also found that parents’ age, level of education, parents' income as well as the number of children with special needs also influenced the level of parenting self-efficacy in both fathers and mothers. They asserted that older parents have more positive parenting experiences compared to parents who are younger and have less experience. Moreover, the greater the number of children with special needs in one family, the more difficult it is for parents to accept all the limitations and carry out the role of care in an effective way.

Further research should be promoted concerning the mediator variables in order to explain their effects more specifically on the social-emotional
abilities of children with special needs. One direction could be to analyze the influence of each dimension of parenting self-efficacy on the social-emotional abilities. A thorough analysis of the various dimensions of parenting self-efficacy could highlight the dimension that is of most influence so that a psychological intervention can be carried out according to needs. Parents who have children with special needs are expected to be able to continue to maintain and improve parenting self-efficacy as the impact of this variable is very significant for the development of their children in all aspects, including the social-emotional skills of children. From the results of this study it appears that the acceptance of parents is not enough to ensure that parents are confident in caring for children with special needs. However, if a parent already has high parenting self-efficacy, this shows that parents have accepted the conditions and limitations of the child. With respect to further research, it would be very helpful to find out if self-efficacy has the same mediating effect on “professional acceptance” for teachers and other non-parental caregivers as it does with parents.

6. Conclusions

This study examined the role of parenting self-efficacy in mediating the effect of parental acceptance on the social-emotional abilities of children with special needs. Based on the results of the current study, it can be concluded that parental acceptance significantly influences the social-emotional abilities of children with special needs. In addition, parenting self-efficacy was found to have a direct significant effect on the social-emotional abilities of children with special needs. Finally, parenting self-efficacy was also found to act as a full mediator in the influence of parental acceptance on the social-emotional abilities of children with special needs.

References


Parenting self-efficacy, parental acceptance and social-emotional abilities in special needs


233


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Parenting self-efficacy, parental acceptance and social-emotional abilities in special needs


Biological and neuropsychological markers of cognitive dysfunction in unipolar vs bipolar Depression: What evidence do we have?

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Abstract

Cognition is a critical aspect of psychopathology. The aim of this review is to evaluate and discuss evidence on the biological and neuropsychological markers of cognitive dysfunction in unipolar and bipolar Depression to improve the differential diagnosis and develop plans of personalized pharmacological treatment. The different use of biological and neuropsychological markers is reviewed and their use to support the clinical process and differential diagnosis is critically examined. While biological markers can help to reduce the risk of misdiagnosis, neuropsychological markers can be assessed more readily and with a less invasive methodology. To this end, additional research on the thresholds differentiating the cognitive dysfunction in unipolar and bipolar Depression should be conducted on specific psychometric tools proposed in this review. Most importantly, future effort should be directed towards the validation of both types of markers specifically for these two populations. Finally, this review contributes to the field by

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focusing on the clinical need of a precise differential diagnosis that, when put in a translational framework, should combine an integration of research and clinical practice allowing for a better understanding of mental health and for evidence-based clinical practice.

*Keywords:* Cognitive dysfunction; Unipolar Depression; Bipolar Depression; Differential diagnosis; Psychometric assessment.
1. Introduction

Cognitive functioning has become of growing interest and has been investigated in a variety of contexts and applications, among which neuropsychological assessment, social cognition, and education (Bajaj, 2020; Osborne-Crowley, 2020; Parrales, Palma, Álava, & Campuzano, 2020).

The understanding of psychopathology has been enriched especially by the focus on human cognitive processes. Nowadays it is well known that mental illness is characterized by significant cognitive impairments that are firmly associated with other affective and behavioral signs and symptoms (Haywood & Raffard, 2017). In schizophrenia, for example, there are alterations in attention, executive functions, language, processing speed, memory and visuospatial ability (Hedges, Farrer, Bigler, & Hopkins, 2019a), while in Obsessive-Compulsive Disorder, specific cognitive strategies are aimed at the management of a sense of guilt (Mancini & Gangemi, 2018), with a lower cognitive flexibility/set shifting and a higher susceptibility to perseveration (Yazdi-Ravandii, Shamsaei, Matinnia, Shams, Moghimbeigi, Ghaleiha et al., 2018).

Disorders that share a disturbance in mood - defined as affective disorders or mood disorders (Ellenbroek & Youn, 2016) - show a particular association with cognitive dysfunction, as deficits in cognition often precede or appear during the early stage of those pathologies and persist after the resolution of emotional symptoms, thereby, contributing to the patient’s overall disability (Hedges, Farrer, Bigler, & Hopkins, 2019b). As the category of “affective disorders” mainly refers to the different kinds of Depressive Disorders and Bipolar Disorders, cognitive dysfunction is observed both in unipolar/bipolar depressive as well as in manic/hypomanic states.

According to the World Health Organization, Depression is ranked as the single largest contributor to global disability, it is the major cause of suicide deaths and affects about 4.4% of the global population; moreover, this number is set to increase (WHO, 2017).

There are different depressive phenotypes but two of them - unipolar and bipolar - represent the most challenging in terms of differential diagnosis (Hirschfeld, 2014). Indeed, long-term follow-up studies have demonstrated that people suffering from Bipolar Disorder spend nearly half of their time (about 40%) in a depressive phase, about 50% of the time in an euthymic phase and only 10% of the time in a manic/hypomanic phase (Judd, Akiskal,
Schettler, Endicott, Maser, Solomon et al., 2002). This is particularly true for Bipolar II Disorder (Judd, Akiskal, Schettler, Coryell, Endicott, Maser et al., 2003). Moreover, bipolar patients usually ask for consultation only when they are depressed (Hirshfeld, Cass, Holt, & Carlson, 2005). These factors together result in late diagnosis or mistreatment, with a negative general outcome regarding the patient’s quality of life and a high overall burden of the disease (Leyton & Barrera, 2010).

Therefore, differential diagnosis is critical. To this end, research on cognition may significantly help the clinician by describing the cognitive profiles of unipolar and bipolar Depression and efforts should be made to include them as part of the diagnostic process in order to personalize pharmacological treatment. In other terms, collecting and differentiating markers of cognitive dysfunction related to the different depressive phenotypes would increase the specificity of the diagnosis and the appropriateness of an adequate treatment.

Starting by acknowledging that unipolar and bipolar Depression are disorders of the brain, and that behavior is the last step of a cascade that started long before problems manifest themselves, we probably should start with the brain, with its wiring and connections, with its metabolism, and with the way it interacts with its surroundings. A lot of variation exists in how the brain is wired and how it functions, but this variation does not exclude the existence of some possible and predictable set of factors that put bipolar and unipolar depressed patients at a different risk for cognitive problems. When crossing a behavioral, emotional, or cognitive threshold, what underlying different thresholds has each patient crossed that has determined his/her vulnerability? What drives the patient’s cognitive dysfunction?

Markers of cognitive dysfunction can be identified either as neuropsychological or as biological, each to be evaluated with their own specific clinical tools.

This review explores the role of neuropsychological and biological markers of cognitive dysfunction in unipolar and bipolar Depression and collects evidence regarding their potential role in strengthening differential diagnosis. Particular attention will be given to the psychometric tools that we might want to include in the assessment of unipolar and bipolar Depression to improve the quality of clinical decision-making and adequately plan the treatment.
2. Depression: Main phenotypes and cognitive dysfunction

The publication of the DSM-5 (APA, 2013) imposed several important changes in the diagnostic categories compared to the previous DSM-IV-TR (APA, 2000), such as, the abolition of the category of “Mood Disorders” (Rodríguez-Testal, Senín-Calderón, & Perona-Garcelán, 2014). In the new Manual, “Bipolar and Related Disorders” and “Depressive Disorders” figure as two distinct categories. The first includes Bipolar I Disorder, Bipolar II Disorder, Cyclothymic Disorder and Disruptive Mood Dysregulation Disorder, while the second includes Major Depressive Disorder (MDD), Persistent Depressive Disorder (Dysthymia), and Premenstrual Dysphoric Disorder.

Given the general aim of this review, it is useful to remind that Bipolar I Disorder must be characterized by a distinct manic episode that may be associated with other periods of Major Depressive Episodes and/or hypomania, whereas Bipolar II Disorder can be diagnosed if there has been at least one episode of hypomania and one episode of Major Depressive Disorder. Major Depressive Disorder, instead, is characterized by a two-week period showing at least either depressed mood or loss of interest or pleasure, associated with other symptoms like changes in appetite, weight, sleep patterns, diminished energy and feelings of worthlessness and excessive guilt. Specifiers and additional criteria of inclusion and exclusion are thoroughly discussed in the DSM-5.

In depressive phenotypes, two fundamental types of cognitive dysfunction can be distinguished: cognitive biases and cognitive deficits (Murrough, Iacoviello, Neumeister, Charney, & Iosifescu, 2011). The first consist of systematic distortions in the processing of information, in terms of selection, interpretation, encoding and retrieval. They influence the way depressed people view themselves, the world and their future and they are best treated by specific psychotherapeutic approaches (Young, Rygh, Weinberger, & Beck, 2014). Cognitive deficits, instead, can be defined as specific impairments in several domains, among which, attention, executive functions, and memory, which represent the main cognitive domains to be considered. They can be detected, measured, and should be taken into consideration to support the diagnosis and the efficacy of treatment. As discussed before, these deficits are expressed in terms of neuropsychological and biological markers. In the next paragraphs, we will present and critically review the markers of cognitive dysfunction in unipolar and bipolar Depression.
3. Markers of cognitive dysfunction in unipolar Depression

3.1. Neuropsychological markers

According to international and Italian psychiatrists, cognitive symptoms represent a relevant dimension of MDD and are among the residual symptoms affecting the risk for relapse (Albert, Brugnoli, Caraci, Dell’Osso, Di Sciascio, Tortorella et al., 2016). Indeed, unipolar Depression is characterized by several neuropsychological markers, which represent a core feature that needs to become a specific target for treatment. For example, SSRI and SNRI antidepressants improve cognitive symptoms independently from their efficacy related to the affective dimension (Castellano, Ventimiglia, Salomone, Ventimiglia, De Vivo, Signorelli et al., 2016). Neuropsychological changes are so obvious that the term “pseudodementia” has been coined to refer to the impaired cognition given the resemblance with neurodegenerative diseases, but instead here it is due to a psychiatric condition (Brodaty & Connors, 2020). Moreover, the DSM-5 includes the “diminished ability to think or concentrate, as well as indecisiveness” as a criterion for a major Depression episode (APA, 2013).

Moderate deficits in executive functions, memory and attention are altered in depressed patients compared to healthy subjects and research has demonstrated that impairment in executive functions and memory persist even after mood symptoms have remitted (Rock, Roiser, Riedel, & Blackwell, 2014). Also, Castellano and co-workers (2020) reported that neurocognitive performance at baseline influenced long-term psychosocial functioning with a specific role played by verbal memory, which predicted the functional outcome after one year in patients who had a partial response to antidepressants (Castellano, Torrent, Petralia, Godos, Cantarella, Ventimiglia et al., 2020).

According to Austin, Mitchell and Goodwin (2001), in MDD there are deficits in attention, verbal and visual memory, executive processes and psychomotor skills, which sums up decades of research on this topic. Also, verbal fluency and attentional set-shifting are impaired in depressed elderly patients (Beats, Sahakian, & Levy, 1996) whereas younger out-patients show similar symptoms with additional deficits in motor speed (Purcell, Maruff, Kyrios, & Pantelis, 1997). Deficits in the Digits backwards task and perseverative responses characterized a sample of patients with endogenous/melancholic Depression (Austin, Mitchell, Wilhelm, Parker, Hickie, Brodaty et al., 1999).
Taken together, the debate with respect to neuropsychological markers is still open and their role in unipolar Depression, either as endophenotypes or as epiphenomena of the pathology (McInerney, Gorwood, & Kennedy, 2016), warrants a more in-depth evaluation.

3.2. Biological markers

Attention towards biological markers of cognitive dysfunction in unipolar Depression is growing fast. The link between Depression and cognitive impairment is so robust, that a lifetime history of Major Depression can be considered as a risk factor for the development of Alzheimer's disease and as a predictor of the conversion from Mild Cognitive Impairment (MCI) to dementia (Steffens, 2012).

Deficits in neurotrophin signaling are observed in Major Depressive Disorder (MDD): reduced plasma levels of BDNF and TGF-β1 - a growth factor and an anti-inflammatory cytokine with key roles in neuroprotection, synaptic plasticity and the formation of new memories - correlate with Depression severity (Caraci, Spampinato, Morgese, Tascedda, Salluzzo, Giambirtone et al., 2018). Moreover, MDD patients display higher levels of proinflammatory cytokines, such as IL-6 and IL-8, and of the tumor necrosis factor-α (TNF-α), which correlate with circulating mitochondrial DNA (mtDNA) (Kageyama, Kasahara, Kato, Sakai, Deguchi, Tani et al., 2018). Signs of inflammation and oxidative stress have led to the hypothesis that the immune system is involved actively in MDD (Maes, Nowak, Caso, Leza, Song, Kubera et al., 2016). Additional data stem from the hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, which leads to higher levels of cortisol in depressed patients and is often associated with inflammation (Pariante, 2017). Lower levels of neurotrophins and higher levels of glucocorticoids together with a heightened inflammation increase Aβ toxicity, hippocampal atrophy and, consequently, cognitive deficits (Caraci, Copani, Nicoletti, & Drago, 2010).

These findings are further strengthened by neuroimaging data. The anterior Cingulate Cortex (ACC) is involved in attention, problem solving, motivation and decision-making (Rushworth, Behrens, Rudebeck, & Walton, 2007), while the Dorsolateral Prefrontal Cortex (DLPFC) is considered critical for cognitive functions (Liao, Feng, Zhou, Dai, Xie, Ji et al., 2012). The ACC, DLPFC and Orbitofrontal Cortex (OFC) have been hypothesized to work together to inhibit a negative emotional response and emotional memory thanks to a cognitive control network, within which
emotional response and memory originate from regions, such as the amygdala and the hippocampus. ACC, DLPFC and OFC appear to be critical biomarkers for cognitive dysfunction in unipolar Depression also when considering data from Electroencephalography (EEG) and Positron Emission Tomography (PET) (Lai, 2019). Furthermore, Magnetic Resonance Imaging (MRI) data indicate the presence of structural changes in recurrent depressed patients with a lower volume of grey matter in the left hippocampus (Samann, Hohn, Chechko, Kloiber, Lucae, Ising et al., 2013). Also, mean depressive symptom scores are associated with reductions in brain volume in the cingulate gyrus and in the OFC, as well as with the rate of a decline in volume of the left frontal white matter (Dotson, Davatzikos, Kraut, & Resnick, 2009).

Taken together, the data regarding biomarkers, do not indicate a clear picture on whether cognitive dysfunction in Depression is part of an underlying and stable neurobiological vulnerability, which would support the neurodevelopmental origins of Depression, or whether cognitive dysfunction occurs only during depressive episodes, as outlined by McInerney and colleagues (McInerney, Gorwood, & Kennedy, 2016), which would support a more immediate environment-related hypothesis with a strong contribution of epigenetics.

4. Markers of cognitive dysfunction in bipolar Depression

4.1. Neuropsychological markers

Cognitive impairment and neuropsychological dysfunction are two fundamental characteristics in patients with Bipolar Disorder, especially in the depressive phase, because the resulting deficits compromise the social, relational and professional capacities of these patients and significantly affect their overall functioning and quality of life (Melloni, Poletti, Vai, Bollettini, Colombo, & Benedetti, 2019).

Significant evidence in the literature has highlighted the relationship between the number of episodes related to mood variability and the severity of cognitive deficits, reporting the presence of structural and neuropsychological changes (Hellvin, Sundet, Simonsen, Aminoff, Lagerberg, Andreassen et al., 2012; Cardoso, Bauer, Meyer, Kapczinski, & Soares, 2015; Passos, Mwangi, Vieta, Berk, & Kapczinski, 2016). In fact, in bipolar patient anomalies related to the white matter (WM), to ventricular
enlargement (Birner, Seiler, Lackner, Bengesser, Queissner, Fellendorf et al., 2015) as well as to the loss of the volume and thickness of the total gray matter (GM) have been observed (Hallahan, Newell, Soares, Brambilla, Strakowski, Fleck et al., 2011; Gildengers, Chung, Huang, Begley, Aizenstein, & Tsai, 2014).

From a neuropsychological point of view, the most important cognitive impairment of bipolar patients, in the depressive phase, are deficits in memory and executive function (Martínez-Arán, Vieta, Colom, Reinares, Benabarre, Gastó et al., 2000; Bearden, Hoffman, & Cannon, 2001; Borkowska & Rybakowski, 2001), even after remission. This data have been confirmed by several other studies, which, other than the aforementioned dysfunctions, also reported of alterations in episodic memory (Sweeney, Kmiec, & Kupfer, 2000), inattention (van der Meere, Börger, & van Os, 2007; Maalouf, Klein, Clark, Sahakian, Labarbara, Versace et al., 2010; Belleau, Phillips, Birmaher, Axelson, & Ladouceur, 2013) in verbal appeal and fine motor skills (Malhi, Ivanovski, Hadzi-Pavlovic, Mitchell, Vieta, & Sachdev, 2007) and finally of dysfunctions related to visual-mnemonic skills and verbal fluency (Martinez-Aran et al., 2000; Harkavy-Friedman, Keilp, Grunebaum, Sher, Printz, Burke et al., 2006; Xu, Lin, Rao, Dang, Ouyang, Guo et al., 2012), which worsen based on the progression of mood-related episodes (Lee, Hermens, Scott, Redoblado-Hodge, Naismith, Lagopoulos et al., 2014; Galimberti, Bosi, Caricasole, Zanello, Dell’Osso, & Viganò, 2020). Furthermore, serious damage is observed in functions of the frontal lobe, which involve visuospatial and visuomotor skills, working memory and, most importantly, executive functioning (Borkowska & Rybakowski, 2001).

Recent research has found a poor performance in verbal memory, working memory, psychomotor coordination and selective assessment in a sample of Bipolar type I depressed patients (Melloni et al., 2019), while marked deficits in episodic memory, in learning and recalling a list of objects, and in encoding information were reported in another study (Dongaonkar, Hupbach, Nadel, & Chattarji, 2019).

As discussed above, the most impaired cognitive function in this phase of Bipolar Disorder, in addition to deficits in memory, seems to be executive functioning: Galimberti and colleagues showed that the centrality of this dysfunction drives the overall cognitive deterioration of the aforementioned patients (Galimberti et al., 2020).

Finally, several authors have explained the relevance of the so-called “suggestive elements” present in the depressive phase of Bipolar Disorder,
which involve psychopathological symptoms and clinical variables and refer to, for example, psychomotor agitation, emotional lability, irritability, insomnia, hyperphagia and rapid thoughts, which, although not involved in the cognitive aspects, influence the recognition of the disorder (Ghaemi, Sachs, & Goodwin, 2000; Yatham, 2005).

Taken together, many of the neuropsychological markers belonging to the depressive phase of Bipolar Disorder are similar to those observed in Unipolar depressive Disorder, albeit with a minimal distinction. Therefore, it is important to further discuss the differences between the two disorders, in order to improve the differential diagnosis and to choose the appropriate therapy that is best fitted to the clinical phenotype of the patient.

4.2. Biological markers

A similarity exists between the biological markers of Bipolar Disorder in the depressive phase with those of unipolar Depression, which concerns the decrease in levels of brain-derived neurotrophic factor (BDNF) levels (Cunha, Frey, Andreazza, Goi, Rosa, Gonçalves et al., 2006; Bourne, Aydemir, Balanzá-Martínez, Bora, Brissos, Cavanagh et al., 2013). In fact, various mood-related episodes negatively affect the homeostatic balance between inflammatory mechanisms, oxidative processes and neuroprotective substances (such as BDNF) and contribute to neuronal apoptosis (Berk, Kapczinski, Andreazza, Dean, Giorlando, Maes et al., 2011; Fries, Pfaffenseller, Stertz, Paz, Dargél, Kunz et al., 2012; Bauer, Pasco, Wollenhaupt-Aguiar, Kapczinski, & Soares, 2014).

Furthermore, in the case of Bipolar Disorder, especially during the depressive phase, the levels of proinflammatory agents are higher, such as for interleukins (IL-6, IL-2R, IL-1beta), the tumor necrosis factor (TNF-α), cellular TNF-α receptors (TNFR1), and CXCL10 serum levels (Barbosa, Huguet, Sousa, Abreu, Rocha, Bauer et al., 2011; Barbosa, Bauer, Machado-Vieira, & Teixeira, 2014; Barbosa, Machado-Vieira, Soares, & Teixeira, 2014; Bauer et al., 2014). In particular, the levels of the pro-inflammatory markers YKL40, sCD40L and hsCRP are higher and these alter the function of monoaminergic systems, such as dopaminergic and serotonergic systems, finally affecting the cognitive and affective functions (Rosenblat, Brietzke, Mansur, Maruschak, Lee, & McIntyre, 2015). The role of adiponectin is relevant as well and plays a basic role in metabolic and inflammatory processes: research has demonstrated that low levels of
adiponectin were associated with the depressive state of bipolar subjects (Platzer, Fellendorf, Bengesser, Birner, Dalkner, Hamm et al., 2019).

Additional evidence comes from studies that support the hypothesis that inflammatory diseases, such as autoimmune thyroiditis, psoriasis, Guillain-Barré syndrome (GBS), autoimmune hepatitis, multiple sclerosis (MS), migraine, rheumatoid arthritis (RA), obesity, atherosclerosis, and type II diabetes mellitus, play a significant role in the genesis of Bipolar Disorder (Kupka, Nolen, Post, McElroy, Altshuler, Denicoff et al., 2002; Edwards & Constantinescu, 2004; McIntyre, Konarski, Misener, & Kennedy, 2005; Bachen, Chesney, & Criswell, 2009; Calkin, Van De Velde, Ruzickova, Slaney, Garnham, Hajek et al., 2009; Eaton, Pedersen, Nielsen, & Mortensen 2010; Han, Lofland, Zhao, & Schenkel, 2011; Hsu, Chen, Liu, Lu, Shen, Hu et al., 2014; Perugi, Quaranta, Belletti, Casalini, Mosti, Toni et al., 2015).

As for unipolar Depression, also for bipolar Depression an involvement of inflammation in metabolic dysfunction has been suggested. In particular, enhanced HPA activity may induce central obesity and insulin resistance (Boutzios & Kaltsas, 2000; Rosenblat et al., 2015).

Research conducted in the field of neuroimaging has contributed greatly to the more accurate analyses of the depressive phase in Bipolar Disorder: bipolar subjects in the depressive phase displayed abnormally high levels of amygdala activity, when exposed to mostly neutral or sad facial expressions, while a reduction was observed in the bilateral amygdala-ventromedial prefrontal cortex (vmPFC) when exposed to happy facial expressions (Almeida, Versace, Mechelli, Hassel, Quevedo, Kupfer et al., 2009).

Other studies, however, observed an increased volume of the lateral and third ventricles (Gulseren, Gurcan, Gulseren, Gelal, & Erol, 2006; Beyer, Young, Kuchibhatla, & Krishnan, 2009; Hallahan et al., 2011; Frey, Andreazza, Houenou, Jamain, Goldstein, Frye et al., 2013; Goldstein & Young, 2013), which became evident only after the occurrence of several mood-related episodes (Strakowski, DelBello, Zimmerman, Getz, Mills, Ret et al., 2002).

Several neurobiological models studying emotional dysregulation have also analyzed the anomalies in the fronto-limbic-subcortical structures in bipolar patients, highlighting that they themselves are part of an increase in bottom-up processes and/or a decrease in top-down processes (Savitz & Drevets, 2009; Phillips & Swarts, 2014). This data are supported by functional magnetic resonance imaging (fMRI) studies in which a reduction in activation in the cortical cognitive brain network and an increased
activation in the ventral limbic brain regions was confirmed in subjects with Bipolar Disorder (Houenou, Fromberger, Carde, Glasbrenner, Diener, Leboyer et al., 2011).

Despite the results achieved, novel studies are needed, including neuroimaging studies, in order to distinguish more clearly the structural and functional differences between unipolar and bipolar Depression and to identify those biological markers that reflect the pathophysiological processes underlying these two disorders (de Almeida & Phillips, 2013).

5. Evidence for differential diagnosis

5.1. Comparing unipolar and bipolar Depression

Carrying out a precise and accurate differential diagnosis between unipolar and bipolar Depression represents a great clinical challenge. The main reason for this concerns not only the higher prevalence of depressive symptoms compared to hypomanic symptoms in bipolar Depression, but also the fact that a significant amount of manic symptoms remain below threshold in both unipolar and bipolar Depression (de Almeida & Phillips, 2013).

Hence, it is easy to understand that the consequences of an incorrect diagnosis could lead to severe problems. For example, if a depressed bipolar patient were treated only with antidepressants, their effectiveness would be reduced since antidepressants should be coupled with mood stabilizers to have the desired therapeutical effect (Goodwin & Consensus Group of the British Association for Psychopharmacology, 2009; Yatham, Kennedy, Parikh, Schaffer, Beaulieu, Alda et al., 2013). Furthermore, inadequate treatment could result in an increased risk of suicide, an easier transition to mania, and an increase in health care costs (Hirschfeld, Lewis, & Vornik, 2003; Perlis, Ostacher, Goldberg, Miklowitz, Friedman, Calabrese et al., 2010; Goodwin, 2012).

Along this line, an accurate screening of the two disorders, from a cognitive point of view, would help to avoid an incorrect diagnosis, which is of fundamental importance (Hirschfeld, 2014).

Biological markers are certainly one of the key issues in the management of patients with unipolar and bipolar Depression and many are common to both ailments. A difference in this sense can be found in serum BDNF levels, which are lower in bipolar patients and higher in unipolar patients and in control subjects (.15 ± .08, .35 ± .08 and .38 ± .12, respectively, p <
Markers of cognitive dysfunction in unipolar vs bipolar Depression

.001) (Fernandes, Gama, Kauer-Sant’Anna, Lobato, Belmonte-de-Abreu, & Kapczinski, 2009). The laboratory cut-off, in fact, equal to .26 pg/ml, is able to sustain the differential diagnosis of the two disorders with an accuracy equal to 88%. Because of this, BDNF could contribute as a predictive marker, as a marker of the presence of the disease or as a surrogate marker (Fernandes, Molendijk, Köhler, Soares, Leite, Machado-Vieira et al., 2015; Polyakova, Stuke, Schuemberg, Mueller, Schoenknecht, & Schroeter, 2015; Sagar & Pattanayak, 2017).

In recent years, the analysis of the neural networks involved in mood disorders, using the neuroimaging data of both structural and functional measures related to the formation of neuronal circuits involved in the processing and regulation of emotions, has been very important (de Almeida & Phillips, 2013).

Thanks to structural magnetic resonance imaging, irregularities in the integrity of the white matter and more specifically of the corpus callosum and the cingulum, characterizing Bipolar Disorder compared to Major Depression, have been observed (Benedetti, Absinta, Rocca, Radaelli, Poletti, Bernasconi et al., 2011; de Almeida & Phillips, 2013; Matsuoka, Yasuno, Kishimoto, Yamamoto, Kiuchi, Kosaka et al., 2017; Repple, Meinert, Grotegerd, Kugel, Redlich, Dohm et al., 2017) and have been associated with alterations in the gray matter volume of the prefrontal cortex and hippocampus (Matsuo, Harada, Fujita, Okamoto, Ota, Narita et al., 2019; Niida, Yamagata, Matsuda, Niida, Uechi, Kito et al., 2019). However, a recent study has shown that depressed bipolar subjects have reduced gray matter volumes in the right hippocampus, in the parahippocampal gyrus, in the fusiform gyrus, in the amygdala, in the insula, in the rolandic and frontal operculum, and in the cerebellum (Vai, Parenti, Bollettini, Cara, Verga, Melloni et al., 2020). Similar results have been reported by Liu and colleagues, who have shown that depressed unipolar patients have an increased ReHo in the right parahippocampal gyrus compared to control subjects. In addition, the ReHo in the right hippocampus of depressed bipolar patients was found to have a larger volume, while the ReHo in the right middle occipital gyrus appeared to be smaller. Finally, bipolar depressed patients displayed a reduction of ReHo in the right inferior temporal gyrus. This suggests that the latter could be considered as an important biological marker in the differential diagnosis of the two disorders (Liu, Li, Zhang, Liu, Sun, Yang et al., 2020). Moreover, as regards regional homogeneity, Liu and colleagues found that subjects with bipolar Depression, compared to unipolar depressed patients, had higher ReHo
values in the right dorsal anterior insular, right middle frontal gyrus, right cerebellum posterior gyrus, and the left cerebellum anterior gyrus (Liu, Ma, Wu, Zhang, Zhou, Li et al., 2013). Liang and colleagues, in contrast, emphasized how bipolar depressed patients displayed higher ReHo values in the thalamus than unipolar depressed patients (Liang, Zhou, Yang, Yang, Fang, Chen et al., 2013).

Other studies, concerning the structural measures of neuroimaging, have contributed to making differential diagnoses more effective, by examining and comparing healthy subjects, unipolar depressed and bipolar depressed patients. These studies helped to discover that bipolar depressed patients present a reduction in fractional anisotropy (FA) in the right uncinate fasciculus (Versace, Almeida, Quevedo, Thompson, Terwilliger, Hassel et al., 2010) as well as an increase in periventricular and deep white matter hyperintensities (DWMH; Silverstone, McPherson, Li, & Doyle, 2003) and a volume reduction in the left habenula (Savitz, Nugent, Bogers, Roiser, Bain, Neumeister et al., 2011). In addition, the anterior cingulate cortex has shown to be a biological marker useful for differential diagnosis: in the depressive phase of Bipolar Disorder, the level of glutamate was higher while in unipolar Depression the level dropped considerably (Yüksel & Öngür, 2010).

Regarding the functional measures of neuroimaging, several studies examined the functionality of the neuronal circuits involved in emotion. Taylor Tavares and colleagues, for example, conducted research with unipolar, bipolar depressed patients and healthy control subjects, in order to analyze whether a reversed learning paradigm could measure the ability to modify a behavior when reinforcement (positive or negative) was changed; unipolar depressed patients reversed their response following negative reinforcement, which appeared to be related to reduced ventrolateral and dorsomedial prefrontal cortical activity, unlike bipolar patients who maintained a normal level of neural activity. In addition, unipolar depressed patients also displayed reduced activity in the ventrolateral prefrontal cortex (VLPFC) during reversal shifting, which was associated with a reduction in the activity of the amygdala in the presence of positive reinforcement (Taylor Tavares, Clark, Furey, Williams, Sahakian, & Drevets, 2008). Another study, which employed an executive control model with emotional distractors and that involved female subjects with bipolar and unipolar Depression, reported that the latter displayed a better developed dorsal anterior mid cingulate cortical activity compared to the other subjects during
the demanding 2-back condition of the model with neutral face distracters (Bertocci, Bebko, Mullin, Langenecker, Ladouceur, Almeida et al., 2012).

Neuropsychological assessment plays a key role in the differential diagnosis between unipolar and bipolar Depression. A number of studies have highlighted the similarity of neuropsychological functioning characterizing both disorders (Sweeney et al., 2000; Gruber, Rathgeber, Bräunig, & Gauggel, 2007; Daniel, Montali, Gerra, Innamorati, Girardi, Pompili et al., 2013). For example, research conducted by Liu and colleagues in a sample of healthy controls, depressed unipolar and bipolar patients showed that the latter two groups had similar impairments in psychomotor speed, working memory, visual memory, verbal fluency and switching of attention with respect to the healthy subjects (Liu, Zhong, Wang, Liao, Lai, & Jia, 2018). The study conducted by Xu and colleagues (2012) showed analogous results. By comparing depressed bipolar I, bipolar II and unipolar patients, a fairly similar cognitive picture emerged regarding dysfunctions in processing speed, visual memory and cognitive functions, although bipolar I patients displayed greater deficits in verbal fluency and executive functions compared to the other patients (Xu et al., 2012). Consistent with these studies, other researchers observed similar clinical and cognitive performances between the two disorders, especially with respect to processing speed (Daniel et al., 2013) and verbal memory (Hermens, Naismith, Redoblado Hodge, Scott, & Hickie, 2010).

In fact, these conclusions are consistent with what has been explained in the previous paragraphs, in which we emphasized that the neuropsychological markers of the two disorders clearly overlap and, in some cases, show the same profile.

In contrast, other studies support the presence of differences in the type of neuropsychological deficits in unipolar and bipolar Depression. Taylor Tavares and co-workers discovered that bipolar depressed people displayed more cognitive deficits than individuals with unipolar Depression (Taylor Tavares, Clark, Cannon, Erickson, Drevets, & Sahakian, 2007). Likewise, the study of Hori and colleagues demonstrated that patients with bipolar Depression had greater deficits in verbal memory and executive functions than patients with unipolar Depression (Hori, Matsuo, Teraishi, Sasayama, Kawamoto, Kinoshita et al., 2012). Furthermore, psychomotor retardation is a particularly clear factor in defining the difference between the two disorders: numerous studies have observed a more evident psychomotor slowdown in bipolar as compared to unipolar Depression (Mitchell, Frankland, Hadzi-Pavlovic, Roberts, Corry, Wright et al., 2011; Motovsky
& Pecenak, 2013). Similarly, attention deficits appear much more marked in depressive Bipolar Disorder (Benazzi, 2006; Mitchell et al., 2011; Gosek, Heitzman, Stefanowski, Antosik-Wójcińska, & Parnowski, 2019).

Borkowska and Rybakowski (2001), on the other hand, analyzed the differences between the two disorders using tools designed to assess the functionality of the frontal lobe. Depressed bipolar patients displayed a higher level of cognitive dysfunction related to the activity of the frontal lobe (in particular, in attention, verbal fluency, spatial planning, and abstract functioning) and presented a significantly reduced performance in non-verbal intelligence compared to unipolar depressed patients. More recent studies (Galimberti et al., 2020) have demonstrated an enhanced mnemonic impairment in subjects with unipolar Depression compared to bipolar Depression, with marked dysfunctions in executive functions being more evident.

Thus far, the nature of the neuropsychological differences between bipolar and unipolar depressed patients is contradictory, which leads to significant difficulties in the differential diagnosis. However, what is certainly known is that subjects with bipolar Depression appear to exhibit greater cognitive impairment than subjects with unipolar Depression.

Consequently, the debate regarding the structure and function of the cognitive and neuropsychological profile between unipolar and bipolar Depression is still open. From a clinical point of view, however, the inclusion of cognitive and neuropsychological analyses should provide valid elements to make a more accurate differential diagnosis between the two described disorders, which up to now have been too often misdiagnosed (Galimberti et al., 2020).

6. Psychometric tools for differential diagnosis

As discussed above, evidence collected thus far is ambiguous and therefore hampers the use of cognitive dysfunction in the differential diagnosis of unipolar and bipolar Depression. If, on the one hand, various authors reported of significant differences between unipolar and bipolar depressed patients regarding cognitive dysfunction, other researchers, on the other hand, observed quantitative and non-qualitative discrepancies, which suggests there is concordance in affirming that the cognitive dysfunctions involved in the two types of Depression are the same, but with a different severity of impairment. Indeed, quantitative differences common to both disorders lead to a lower performance in patients with bipolar Depression.
Based on the accumulating empirical evidence, but more importantly because of the paucity in neuropsychological tests that support a scrupulous differential diagnosis between the two disorders, we suggest the following.

As a first step, we propose to perform research on the calibration and validation of the psychometric tests presented in the next paragraphs and to define the thresholds differentiating unipolar from bipolar depressive cognitive dysfunction. These (domain-specific) cut-off scores will then allow us to distinguish the cognitive deficits framed within a unipolar or bipolar Depression from a quantitative point of view.

A large review of the previous literature has helped us understand which tests detect quantitative differences between patients suffering from one or the other disorder. As a second and last step, we thus suggest to add other psychometric tools to discriminate between the presence or absence of specific neuropsychological deficits. After the suggested calibration mentioned above, these tools should become an essential part of the psychometric strategies in support of the differential diagnosis between unipolar and bipolar Depression.

6.1. Memory

Deficits in memory appear to be a neuropsychological dysfunction common to both unipolar and bipolar Depression although it is more deficient in bipolar depressed patients (Murphy & Sahakian, 2001; Mansell, Colom, & Scott, 2005).

After a careful review of the literature, we have selected several psychometric tools useful for differential diagnosis.

A first important tool is the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987). The task is simple: the experimenter reads a list of 16 words (list A), aloud and at intervals of one second, at the end of which the participant will have to repeat the words he/she remembers in any order. The 16 words, which are part of 4 large semantic clusters (tools, fruit, clothing, spices and aromatic herbs), are not consecutive in the same category. Subsequently, list B is presented to the participants. This is a list of “interferences” that contains two categories of list A and two random categories, not shared by the former. Neither list contains words common to both. The repetition of the words contained in list A is requested immediately (short delay) as well as after 20 minutes (long delay). The test ends with a recognition exercise, in which 44 words are presented to the subject that must be categorized by him/her as target words or distractors.
The CVLT has proved to be highly discriminating not only for mnemonic deficits in general but specifically for episodic memory, as well as for dysfunctions related to verbal learning, because the test collectively assesses the encoding, the recall and the recognition of the elements presented. Apart from measuring the number of elements that a subject can learn, it also stresses the strategies and techniques that the subject uses to learn new information.

Another useful tool to analyze deficits related to visual-spatial memory is the Corsi Test (Kessels, van Zandvoort, Postma, Kappelle, & de Haan, 2000). It consists of a wooden tablet on which 9 asymmetrical cubes are glued facing the side of the experimenter. The experimenter first touches the cubes with one finger, forming a standard sequence of increasing length, which the subject will have to reproduce later based on what he/she remembers of the path. The test is useful especially for depressed bipolar patients, who have visual-spatial abilities that are more compromised than unipolar depressed patients.

Regarding deficits involving working memory, the Mini Mental State Examination (MMSE) is a very useful test (Folstein, Folstein, & McHugh, 1975). The MMSE is composed of 30 questions, which, in addition to verifying the dysfunctions in working memory, also analyze problems related to space-time orientation, attention, language and constructive praxis. The MMSE represents an excellent tool for differential diagnosis because once calibrated for unipolar and bipolar Depression, it would offer a wider range of cognitive areas to be evaluated, allowing to assess the differences between the two forms of depression more accurately.

Finally, the Rey Auditory Verbal Learning Test (RAVLT) is an excellent tool to discriminate among mnemonic disorders, especially those related to verbal memory (Rey, 1958; Taylor, 1959). The RAVLT consists of 7 tests. In the first test, the examiner reads a list of 15 words that the subject must immediately repeat, and this is repeated 4 times. In the sixth test, the administrator distracts the subject with visuospatial tasks for 15 minutes, to then make him/her repeat the words read previously. If the subject cannot remember them all, another 45 words will be presented to him (30 distractors together with 15 of the first test) and he/she will be asked to list them again. The test is very useful not only because it discriminates deficits in verbal memory, but also because it analyzes verbal learning, which is strongly compromised in subjects with bipolar Depression and, therefore, useful in a differential diagnosis.
6.2. Executive functions

Executive functions, like memory, seem to be particularly deficient in patients with bipolar Depression (Hori et al., 2012).

The Frontal Assessment Battery (FAB; Dubois, Slachevsky, Litvan, & Pillon, 2000) is a sophisticated test that we suggest to be included in the neuropsychological evaluation of patients with bipolar and unipolar Depression. The test battery is divided into 6 cognitive and behavioral tasks, which are the following: conceptualization of similarities, phonemic lexical fluency, motor programming, response to conflicting instructions, task on inhibitory control (go-no-go) and prehension behavior. The FAB is recommended because it discriminates the overall functioning of all executive functions, thanks to its 6 cognitive tasks.

Another important battery to be included to test executive function is the Behavioral Assessment of the Dysexecutive Syndrome (BADS; Wilson, Alderman, Burgess, Emslie, & Evans, 1996). The BADS is an excellent tool because it is composed of various tests that globally evaluate many aspects of executive functions, using an ecological approach that reproduces contexts and problems similar to those encountered in everyday life. The 6 cognitive tasks to be performed include: test of the rule change of cards, action planning test, key search test, test of cognitive estimates, zoo map test and modified test of the 6 elements.

Finally, an important practical test to be included for the evaluation of the aforementioned functions is the Tower of London Test (Allamanno, Della Sala, Laiacona, Pasetti, & Spinnler, 1987). It consists of a tablet with three vertical rods positioned in ascending order, on which 3 balls of different colors are inserted in a specific order. The rods are long enough to accommodate one, two or three balls. The subject will have to move the balls, one at a time, in order to reach an arrangement previously established by the administrator. This test helps to understand the subjects' abilities regarding strategic decision-making processes and the planning of effective solutions as well as the capacity to inhibit impulsiveness as it has the objective of solving a specific task while being constraint by specific rules.

6.3. Attention

We carefully reviewed the literature and attention was shown to be markedly involved in both unipolar and bipolar Depression. To test attention and attention-related functions, it is essential to carefully choose specific
neuropsychological tests that are able to discriminate the presence or absence of any attention-related deficits.

To this end, we propose the following two tests for the assessment of attention in bipolar and unipolar depressed patients.

The first is the Trail-making Test (TMT-A and TMT-B) (Reitan, 1958), which can be performed on paper or on a computer. In the TMT-A version, the 25 stimuli are numbers that the subject must connect with a line in an increasing manner, in the shortest possible time. Version B (TMT-B), on the other hand, is characterized by stimuli, which are both numbers and letters; in this case the subject, starting from number 1, alternates his/her ability to connect, in an increasing way, a number and a letter. This test not only discriminates deficits related to attention, but it is also sensitive to the detection of dysfunctions related to spatial planning skills. Several studies have used the Trail-making Test to make a differential diagnosis. For example, Xu and colleagues highlighted that bipolar depressed patients presented a poorer attention and visual-motor performance than unipolar depressed patients (Xu et al., 2012). Borkowska and Rybakowski (2001), on the other hand, noticed a tendency in depressed bipolar patients to obtain poorer results on the TMT-B than unipolar patients.

The second test we propose is the Stroop Color Word Interference Test (Golden, 1978). It is a test in which the subject must name the ink color with which the names of different contrasting colors are written. To do this, it is necessary to inhibit the automatic tendency to read the color name rather than focusing on the color of the ink itself. Borkowska and Rybakowski used the Stroop test to analyze differences between the two types of depression regarding attention and observed that also in this case the scores of depressed bipolar patients were lower than those of unipolar patients (Borkowska & Rybakowski, 2001).

6.4. Abstract reasoning

Abstract reasoning, which represents one of the most important cognitive abilities in carrying out activities related to daily life, is compromised in both unipolar and bipolar Depression.

One of the most valid and reliable tests assessing this neuropsychological function is the Wisconsin Card Sorting Test (WCST; Monchi, Petrides, Petre, Worsley, & Dagher, 2001). The WCST uses a deck of cards called “response” cards, which must be combined to the “stimulus” cards, according to an entirely personal criterion that changes from subject to

258
Markers of cognitive dysfunction in unipolar vs bipolar Depression

subject. During the test, the administrator is allowed to give only a (minimal) feedback regarding the strategies used by the patient who, thanks to the feedback, will identify the most correct classification criteria. Among the criteria for one type of classification, the administrator switches to another criterion without informing the subject. The subject's task now is to develop a new classification strategy. The WCST is an excellent test not only because it is able to discriminate deficits related to abstract reasoning, but also because it specifically examines the frontal functions of the subject, which are more compromised in bipolar depressed patients (Borkowska & Rybakowski, 2001). In addition, the WCST helps to evaluate the degree of flexibility of patients towards problem solving and the strategies used in everyday life to cope with difficulties. From this point of view, it would be important to analyze the problem solving skills of unipolar and bipolar depressed people and to include the WCST to help the differential diagnosis of the two disorders: Borkowska and Rybakowski (2001) observed a worse performance on the WCST in depressed bipolar patients as compared to unipolar depressed patients.

6.5. Verbal fluency and processing speed

Finally, the Wechsler Adult Intelligence Scale (WAIS-IV) can turn useful to evaluate dysfunctions in verbal fluidity and processing speed. The WAIS is made up of 15 subtests, divided into 4 dimensions: visual-perceptual reasoning, working memory, verbal comprehension, and processing speed. The last two dimensions are those that are more specifically connected to our purpose.

Verbal comprehension is characterized by the subtests: Similarities, Vocabulary, Information and Understanding. The index of this dimension predicts the results regarding crystallized intelligence (connected to the knowledge acquired in the educational and the school context) and concerns contextualized learning within the social environment.

Processing speed, on the other hand, is characterized by the subtests: Search for symbols and Cipher and Cancellation, whose index mainly measures the speed with which the visual stimuli and the manual motive responses are performed by the subject.

This test offers important advantages because it not only helps to assess the dysfunctions related to verbal fluency and speed of processing, which are both severely compromised in the two types of Depression, but also helps to give a general judgment concerning the patient's intellectual
functioning and allows for the analyses of other possible deficits related to cognitive and intellectual abilities. In the end the results from all the different domains will provide us with the necessary insight into the patients strengths and needs that will lead to the development and planning of individually tailored interventions for the recovery or enhancement of the patient’s skills.

7. Conclusions

Depression is a complex disorder causing long-term disability, when not treated adequately. In this review, evidence related to the difference between unipolar and bipolar Depression was collected and presented, with a specific focus on cognitive dysfunction. As the literature suggests, biological markers can help to reduce the risk of misdiagnosis, but neuropsychological markers can be assessed more quickly, more easily and with a methodology that is less invasive. To this end, additional research on thresholds differentiating the cognitive dysfunction in unipolar and bipolar Depression should be conducted on the psychometric tools proposed in this review.

As stated by Cammisuli and Pruneti (2018), the psychopathology of cognition is now focused on how cognitive dysfunction is related to the origin and development of psychiatric conditions, as cognitive processes are intrinsically linked to emotional and relational functioning. The scope of this review was to contribute to the field focusing on the clinical need of a precise differential diagnosis that, when put in a translational framework, should combine an integration of research and clinical practice allowing for a better understanding of mental health and for evidence-based clinical practice.

Including biomarkers is not going to give us a definite answer, but may help to identify risk, not the cause of the cognitive dysfunction. Furthermore, given the extreme complexity of the problem, most biological risk factors may contribute together with other risk factors (pertaining to other dimensions) to a small amount of risk but may help to explain and predict a substantial part of present and future cognitive disability. By using a combination of neurocognitive and biological markers, we may be able to redefine how to think about cognitive dysfunction in unipolar and bipolar Depression.

Patients diagnosed with Depression often develop clinically meaningful deficits in attention, information processing speed, executive functions, such as working memory, and emotional and psychosocial functioning. These
deficits can have a detrimental impact on their quality of life. Failure to comprehensively assess and closely monitor the specific cognitive signs and symptoms of unipolar and bipolar depressed patients may lead to confusion or misattribution surrounding their day-to-day struggles. Therefore, an early detection by combining biomarkers with appropriate neuropsychological indicators and cut offs for cognitive dysfunction may help us to intervene in a timely and appropriate manner using the right treatment for each individual patient. To this end, this review contributes to an empirically founded use of psycho-diagnostic tools in a field that is yet to be fully investigated.

References


Markers of cognitive dysfunction in unipolar vs bipolar Depression


Markers of cognitive dysfunction in unipolar vs bipolar Depression


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

Febronia Riggio¹, Santo Di Nuovo¹ & Giuseppe Zappalà²

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, Aghakhanian, 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 Beijsterveldt, Haukka, Livannainen, Saarikemppainen, 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,
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 remodeled 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, & Hammeneke, 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

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 109)</th>
<th>Women (n = 137)</th>
<th>Total (n = 246)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right-handers</td>
<td>47 (43.12%)</td>
<td>62 (45.25%)</td>
<td>109 (44.31%)</td>
</tr>
<tr>
<td>Left-handers</td>
<td>13 (11.93%)</td>
<td>27 (19.71%)</td>
<td>40 (16.26%)</td>
</tr>
<tr>
<td>Forced right-handers</td>
<td>49 (44.95%)</td>
<td>48 (35.04%)</td>
<td>97 (39.43%)</td>
</tr>
</tbody>
</table>

\(\chi^2 = 3.84, df = 2, p = .15\)
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**

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

\(\chi^2 = 1.51, df = 4, p = .82\)

*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*

![Graph showing difference of mean MoCA score for manual preference in the subsample of Mild Cognitive Impairment.](image)

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

<table>
<thead>
<tr>
<th>Subject’s handedness</th>
<th>Familiar handedness</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Right-handed</td>
<td>64 (60.4%)</td>
<td>24 (25.8%)</td>
<td>88 (44.2%)</td>
<td></td>
</tr>
<tr>
<td>Left-handed</td>
<td>7 (6.6%)</td>
<td>21 (22.6%)</td>
<td>28 (14.1%)</td>
<td></td>
</tr>
<tr>
<td>Forced right-handed</td>
<td>35 (33.0%)</td>
<td>48 (51.6%)</td>
<td>83 (41.7%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>106</td>
<td>93</td>
<td>199</td>
<td></td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Cognitive Decline</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No familial left-handed</td>
<td>43 (21.61%)</td>
<td>28 (14.07%)</td>
<td>35 (17.59%)</td>
<td>106 (53.27%)</td>
</tr>
<tr>
<td>Familial left-handed</td>
<td>43 (21.61%)</td>
<td>33 (16.58%)</td>
<td>17 (8.54%)</td>
<td>93 (46.73%)</td>
</tr>
</tbody>
</table>

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

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.

References


The impact of COVID-19 confinement on the neurobehavioral manifestations of people with Major Neurocognitive Disorder and on the level of burden of their caregivers

Simonetta Panerai¹, Giuseppina Prestiani¹, Sabrina Musso¹, Stefano Muratore¹, Domenica Tasca¹, Valentina Catania¹, Donatella Gelardi¹ & Raffaele Ferri¹

Abstract

The long-term consequences of confinement at home due to the COVID-19 pandemic are not yet known; however, an exacerbation of the neurobehavioral symptoms of patients with dementia and an increase in their caregiver burden are conceivable. The aims of this study were to investigate any changes in the neuropsychiatric symptoms of patients with Major Neurocognitive Disorder as well as in the levels of burden and distress of their caregivers due to COVID-19 confinement, and to detect any relationship between the changes in patients and their caregivers. A “pre-post” study was carried out by means of a semi-structured telephone interview, which was administered to 128 caregivers of patients with dementia. The interview included patient and caregiver demographic information, the Neuropsychiatric Inventory-Questionnaire (NPI-Q) and the Caregiver Burden Inventory (CBI). Results showed an increased risk for burning out of caregivers by about

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10%. Statistically significant differences were found between the conditions prior to lockdown (pre-lockdown) and during lockdown in both the CBI and the NPI-Q distress scale. Neuropsychiatric symptoms in patients with dementia significantly increased as well. Results have a practical implication for the organization of public and private support services.

Keywords: Caregiver burden; Caregiver distress; COVID-19; Major Neurocognitive Disorder; Neurobehavioral manifestations.
1. Introduction

The COVID-19 pandemic is having a remarkable impact on the physical and mental health of the general population (Fagiolini, Cuomo, & Frank, 2020; Wang, Li, Barbarino, Gauthier, Brodaty, Molinuevo et al., 2020), and may produce a wide range of neurological and neuropsychiatric manifestations through complex mechanisms of neuroinvasion and neuroinfection (Pennisi, Lanza, Falsone, Fisicaro, Ferri, & Bella, 2020). It has changed habits, routines, and lifestyles, affecting human relationships, and has had a deep impact on the economies of countries at a global scale. In Italy at the end of July the number of people affected by SARS-CoV-2 had exceeded 245,000 and over 35,000 died (median age 80 years, interquartile range 74-88). In Sicily, the number of infected people was over 3,000 and the victims were over 280; the local government established four red zones (approximately, from March 24th to May 4th). A recent study on the Italian general population (Moccia, Janiri, Pepe, Dattoli, Molinaro, De Martin et al., 2020) has indicated that a relevant proportion of the population may have experienced psychological distress during the COVID-19 outbreak. Another Italian study (Cerami, Santi, Galandra, Dodich, Cappa, Vecchi et al., 2020) found that both distress and loneliness affected the perception of the severe impact of COVID-19 on health. Older adults, particularly those with dementia, were shown to be especially vulnerable during crisis times, because of their cognitive and functional impairments (Boutoleau-Bretonnière, Pouclet-Courtemanche, Gillet, Bernard, Deruet, Gouraud et al. 2020; Wang et al., 2020). Some measures have been put into practice by the governments of several countries, including Italy, in order to reduce the risk of SARS-CoV-2 infection: for example, social distancing, prohibition of displacement to and from certain countries, suspension of social, religious, and care activities (including outpatient visits in public and private hospitals and outpatient rehabilitation, which might potentially attenuate neuropsychiatric symptoms associated with dementia and partially reduce the speed of decline; Buschert, Bokde, & Hampel, 2010). These measures may have resulted in an increased sense of loneliness, social isolation and discomfort in frail people with dementia and their caregivers. Coping with the psychological and behavioral symptoms of dementia by the caregivers frequently produces an increase in distress (Donaldson, Tarrier, & Burns, 1998; Marvardi, Mattioli, Spazzafumo, Mastriforti, Rinaldi, Poldori et al., 2005; Allegri, Sarasola, Serrano, Taragano, Arizaga, Butman et al., 2006; Boutoleau-Bretonnière, & Vercelletto, 2009; Raggi, Tasca, Panerai, Neri, &
Ferri, 2015); caregivers are often alone in facing their anxiety and their burden is also frequently correlated with the onset of depressive symptoms (Sherwood, Given, Given, & von Eye, 2005). In a period of extreme discomfort, the burden and distress may increase, also due to the lack of formal and informal supports. The long-term consequences of the confinement are not known yet, but we may hypothesize an exacerbation of the neurobehavioral symptoms in patients and an increase in the self-perceived burden of caregivers.

2. Aims and hypothesis

Our study was aimed to: (1) investigate the presence of any changes in the neuropsychiatric symptoms of patients with dementia as well as in the levels of burden and distress of their caregivers, following the confinement decided by the local authority in order to limit the pandemic spread; (2) detect a potential relationship between the changes in patients and caregivers. The long-term consequences of the confinement are not known yet, but we may hypothesize an exacerbation of the neurobehavioral symptoms in patients and an increase in the self-perceived burden of caregivers.

3. Methods

3.1. Study Design

A “pre-post” study was carried out between April 14th and May 16th 2020 in which the impact of the confinement during the Covid-19 pandemic on the neurobehavioral manifestations of patients with Major Neurocognitive Disorders (M-NCD; American Psychiatric Association, 2013) as well as in the levels of distress and burden of their caregivers was investigated.

3.2. Sample

A convenience sampling was chosen to facilitate the recruitment of available caregivers; patients were identified among those living in Sicily and diagnosed in our Institute during the six months preceding the national quarantine imposed on March 9th 2020 by the Italian Government. Diagnoses were made by a multidisciplinary team on the basis of the DSM 5 (American Psychiatric Association, 2013) criteria for M-NCD. During the
diagnostic process, dementia was staged using the Clinical Dementia Rating Scale (CDR) (Hughes, Berg, Danziger, Coben, & Martin, 1982); any comorbidities were identified using the Cumulative Illness Rating Scale (CIRS index; Parmelee, Thuras, Katz, & Lawton, 1995).

Among all potential participants ($N = 134$), 128 accepted to participate in the study. The socio-demographic characteristics of caregivers ($N = 128$) are shown in Table 1. The clinical and socio-demographic characteristics of patients with M-NCD ($N = 128$) are shown in Table 2.

### Table 1 – Socio-demographic characteristics of caregivers

<table>
<thead>
<tr>
<th>Variables</th>
<th>Median (IQR), or N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, males/females</td>
<td>34/94</td>
</tr>
<tr>
<td>Chronological age, years</td>
<td>57.5 (47-70)</td>
</tr>
<tr>
<td>Level of instruction, years</td>
<td>8 (8-13)</td>
</tr>
<tr>
<td>Marital status, married/cohabiting/single/separated</td>
<td>102/2/20/4</td>
</tr>
<tr>
<td>Relationship degree with relatives with dementia</td>
<td>62/57/9</td>
</tr>
<tr>
<td>Medical pathology</td>
<td></td>
</tr>
<tr>
<td>- hypertension</td>
<td>26</td>
</tr>
<tr>
<td>- headache, pain</td>
<td>13</td>
</tr>
<tr>
<td>- cardiovascular disorders</td>
<td>11</td>
</tr>
<tr>
<td>- endocrinological pathologies</td>
<td>7</td>
</tr>
<tr>
<td>- infected by Covid 19</td>
<td>0</td>
</tr>
<tr>
<td>- other pathologies</td>
<td>29</td>
</tr>
<tr>
<td>Pre-Covid occupational status</td>
<td></td>
</tr>
<tr>
<td>- employed/unemployed/retired</td>
<td>39/56/33</td>
</tr>
<tr>
<td>Dismissal during pandemic</td>
<td>8</td>
</tr>
</tbody>
</table>

IQR = Interquartile range
Table 2 – Clinical and socio-demographic characteristics of patients with M-NCD

<table>
<thead>
<tr>
<th>Variables</th>
<th>Median (IQR), or N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, males/females</td>
<td>61/67</td>
</tr>
<tr>
<td>Chronological age, years</td>
<td>76 (68.75-82)</td>
</tr>
<tr>
<td>Clinical Dementia Rating scale (CDR)</td>
<td></td>
</tr>
<tr>
<td>- 1 = mild/2 = moderate/3-4 = severe</td>
<td>59/47/22</td>
</tr>
<tr>
<td>Dementia type</td>
<td></td>
</tr>
<tr>
<td>- AD/FTD/VD/PD/Mixed/Other</td>
<td>31/8/42/5/7/35</td>
</tr>
<tr>
<td>Patient infected by Covid-19</td>
<td>0</td>
</tr>
<tr>
<td>Drug assumption</td>
<td>128</td>
</tr>
<tr>
<td>Cumulative Illness Rating Scale, Comorbidity index</td>
<td>2 (1-3)</td>
</tr>
<tr>
<td>Cumulative Illness Rating Scale, Severity index</td>
<td>1.3 (1.15-1.46)</td>
</tr>
<tr>
<td>Decrease of memory skills during confinement*</td>
<td>50 (39%)</td>
</tr>
<tr>
<td>Decrease of self-care skills during confinement*</td>
<td>39 (30.5%)</td>
</tr>
<tr>
<td>Living conditions during confinement</td>
<td></td>
</tr>
<tr>
<td>- maintained routines (daily habits, mealtimes, bedtime)</td>
<td>111 (86.7%)</td>
</tr>
<tr>
<td>- planned day</td>
<td>66 (51.6%)</td>
</tr>
<tr>
<td>- possibility to go out (backyard, home garden)</td>
<td>54 (42.2%)</td>
</tr>
<tr>
<td>- maintained formal and informal support for assistance</td>
<td>92 (71.9%)</td>
</tr>
</tbody>
</table>

* Data based on information from the caregivers.
IQR = Interquartile range; AD = Alzheimer’s Disease; FTD = Fronto-Temporal Dementia; VD = Vascular Dementia; PD = Parkinson’s Dementia

3.3. Instruments

The semi-structured interview consisted of three parts: (1) the collection of personal data of patients and their caregivers and information about their living conditions during the lockdown; (2) how caregivers judged the impact of confinement on the cognitive and adaptive skills of their relatives (patients) with dementia, and (3) the administration of two questionnaires, the Neuropsychiatric Inventory-Questionnaire (NPI-Q; Kaufer, Cummings, Ketchel, Smith, MacMillan, Shelley et al., 2000) and the Caregiver Burden Inventory (CBI; Novak, & Guest, 1989).

The NPI-Q is used to detect the presence or absence of neuropsychiatric symptoms and their severity in patients with dementia. It assesses 12
COVID-19 pandemic impact on N-MCD

behavioral symptoms (delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, aberrant motor activity, sleep and night time behavior disorder, appetite and eating disorder); the severity scores range from 1 to 3 points (mild-to-severe), whereas the associated caregiver distress from 0 to 5 points (from “no distress” to “extreme distress”). Test-retest correlations between the symptoms and distress scores are .80 and .94, respectively ($p < .0001$ for both). The interscale correlation between the Neuropsychiatric Inventory total score and the NPI-Q severity total score is .91, while the interscale correlation between caregiver distress ratings is .92 (Cummings, Mega, Gray, Rosenberg-Thompson, Carusi, & Gornbein, 1994).

The CBI includes a total of 24 items divided into five subscales: Time Dependence, describing the restriction of the caregivers personal time; Developmental burden, referred to the caregivers sense of failure about the expected life-course, hopes and intentions, with respect to their peers; Physical, referred to the caregivers sense of fatigue and damage to their own physical health; Social, referring to family relationship and job performance, and Emotional, describing caregivers negative feelings due to the patient’s inappropriate behaviors. Each item is scored on the basis of a Likert-type scale ranging from 0 (strongly disagree) to 4 (strongly agree). A total score of 36 indicates a risk for burning out, whereas scores near or slightly above 24 indicate the need to take a break and rest (Raggi et al., 2015). The alpha factor of internal consistency is .73 - .86. The high internal consistency of the test (alpha = .80) has also been validated in the Italian context by the study conducted by Marvardi and colleagues (2005).

3.4. Procedure

The semi-structured telephone interview was administered to the caregivers by clinical psychologists working at the Brain Aging Department of our Institute, specifically devoted to people with dementia and acquired cognitive impairment. Caregivers were given a first phone call in order to be informed about the purpose and characteristics of the interview and the tasks required by the study protocol, the probable duration of the phone call, the confidentiality of data to be collected, the risk and benefits of the study, the invitation to decide whether to participate or not, the researcher contact information. After obtaining an informed consent by clicking a box, a second phone call was scheduled to carry out the proper interview to each participant. For the NPI-Q and the CBI, caregivers were required to score
the items in relation to the pre-lockdown period (four weeks) and during the lockdown (four weeks). Questionnaires were administered in the time interval April 14th - May 16th, 2020, i.e. between lockdown phase 1 and the beginning of phase 2 (that started in Italy on May 4th, 2020). During phase 2, displacements and access to public places for elderly and frail people were rather limited as well. Approval was obtained from the Local Ethics Committee “Comitato Etico IRCCS Sicilia–Oasi Maria SS.” and was done in accordance with the Helsinki Declaration of 1975.

3.5. Data analysis

Asymmetry and kurtosis calculations did not show any normal distribution for most of the variables considered in the study so that non-parametric statistics were used. The significance level was set at \( p < .05 \). Differences between the conditions of pre-lockdown and during lockdown in the neurobehavioral manifestations of patients, as well as in distress and burden of family caregivers, were analyzed by means of the Wilcoxon matched pairs test. Effect sizes were calculated by using the \( r = \frac{z}{\sqrt{N}} \) formula, where \( N \) is the total number of participants (\( r = .1 \), small effect size; \( r = .3 \), medium effect size; \( r = .5 \), large effect size). The Chi square test was used to evaluate differences between the number of worsened and stable patients or caregivers, grouped on the basis of opposite conditions experienced during the confinement, for example maintenance/non-maintenance of cognitive and self-care skills by patients, or cessation/maintenance of formal and informal support for assistance, cessation/maintenance of daily routines. The effect sizes were calculated by using the Cramer’s \( V \) test, where scores \( \leq .2 \) indicate a small effect size, scores between .2 and \( \leq .6 \) a moderate effect size, and \( > .6 \) a strong effect size. Correlation analysis of differences between the phases of pre- and during lockdown on the CBI (total and subsection scores) and the NPI-Q (severity and distress scales) were carried out with the Spearman’s test.

4. Results

As far as caregivers are concerned, CBI scores indicated a risk for burning out (score \( \geq 36 \)) in 12.5% of individuals (\( N = 16 \)) in the pre-lockdown condition and in 21.9% (\( N = 28 \)) during lockdown, with an increase of about 10%. Statistically significant differences (Tab. 3) were found between pre-and during lockdown CBI total and subsection scores,
with a large effect size in total scores and Physical burden and a medium effect size in Time Dependence and Developmental burden.

**Table 3** – Caregiver Burden Inventory (CBI) and Neuropsychiatric Inventory-Questionnaire (NPI-Q) scores in the conditions of pre- and during lockdown and statistically significant differences in the whole sample

<table>
<thead>
<tr>
<th></th>
<th>Pre-lockdown Median (IQR)</th>
<th>During-lockdown Median (IQR)</th>
<th>Wilcoxon’s test</th>
<th>z</th>
<th>p ≤</th>
<th>effect size, r</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Caregivers (N = 128)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CBI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Time dependence</td>
<td>10 (5-15)</td>
<td>11 (6-16)</td>
<td>5.51</td>
<td>.000001</td>
<td>.49</td>
<td></td>
</tr>
<tr>
<td>- Developmental burden</td>
<td>4.5 (1-9)</td>
<td>5 (1-10)</td>
<td>4.56</td>
<td>.000005</td>
<td>.4</td>
<td></td>
</tr>
<tr>
<td>- Physical burden</td>
<td>2 (0-5)</td>
<td>4 (0-6.5)</td>
<td>6.16</td>
<td>.000001</td>
<td>.545</td>
<td></td>
</tr>
<tr>
<td>- Social burden</td>
<td>0 (0-1)</td>
<td>0 (0-2)</td>
<td>2.60</td>
<td>.009</td>
<td>.23</td>
<td></td>
</tr>
<tr>
<td>- Emotional burden</td>
<td>0 (0-1)</td>
<td>1 (0-2)</td>
<td>2.97</td>
<td>.003</td>
<td>.26</td>
<td></td>
</tr>
<tr>
<td>- Total scores</td>
<td>18.5 (9-28)</td>
<td>21 (11-34)</td>
<td>6.97</td>
<td>.000001</td>
<td>.61</td>
<td></td>
</tr>
<tr>
<td><strong>NPI-Q</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Distress</td>
<td>4 (1-8)</td>
<td>5 (2-9)</td>
<td>2.66</td>
<td>.008</td>
<td>.23</td>
<td></td>
</tr>
<tr>
<td><strong>Patients (N = 128)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NPI-Q</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Symptoms</td>
<td>3 (1-4)</td>
<td>3 (2-5)</td>
<td>4.83</td>
<td>.000001</td>
<td>.43</td>
<td></td>
</tr>
<tr>
<td>- Severity</td>
<td>3 (1-6)</td>
<td>5 (2.75-8)</td>
<td>4.94</td>
<td>.000001</td>
<td>.44</td>
<td></td>
</tr>
</tbody>
</table>

IQR = Interquartile range; CBI = Caregiver Burden Inventory; NPI-Q = Neuropsychiatric Inventory-Questionnaire

Social and emotional burden also significantly increased, as well as the NPI-Q distress; however, the relative effect sizes were small. The statistical analysis (Chi Square test) carried out on the differences between the number of worsened and stable caregivers, grouped into opposite categories based on opposite life conditions experienced during confinement, showed the following results (Tab. 4): the CDR 2 severity dementia condition was associated with increased distress (NPI-Q distress) in a larger number of caregivers when compared to CDR 1 and CDR 3-4; the condition of decreased memory skills in the patients produced an increase in both distress
(NPI-Q distress) and psychophysical burden (CBI) in a larger number of caregivers when compared with the condition of stable memory skills.

The patients’ condition of decreased self-care skills, the cessation of formal and informal support, the inability to maintain daily routines, as well as the non-planned days all brought about to an increased psychophysical burden (CBI) in a higher number of caregivers when compared with the opposite conditions (stable self-care skills, maintenance of formal and informal support, maintenance of daily routines and planned days, respectively). In the condition regarding the possibility/impossibility to go out, no statistically significant difference was found between the number of worsened and stable caregivers in terms of burden and distress scores.

The severity of the neuropsychiatric symptoms of patients significantly increased (Tab. 3), with a medium effect size. The amount of symptoms, as detected in the conditions of pre- and during lockdown, significantly increased as well, showing a $p$ value of .000001, and a medium effect size ($r = .43$). The same statistical test applied to subgroups on the basis of the rating of dementia severity showed significantly increased neuropsychiatric symptoms in CDR 1 (symptoms amount: $p = .0011$, $r = .42$; symptoms severity: $p = .0016$, $r = .41$), and CDR 2 subgroups (symptoms amount: $p = .002$, $r = .44$; symptoms severity: $p = .00019$, $r = .54$).

The symptom severity turned out to be increased in a large number of patients, but only among those who showed decreased memory skills, when compared to those who maintained stable memory skills (Tab. 4). No statistically significant differences were found between the number of worsened and stable patients regarding any of the other conditions.

Statistically significant positive correlations (Spearman’s test; $p < .05$) were found between the periods of pre- and during lockdown in the NPI-Q distress scale and in the CBI total scores, as well as in the Physical and Emotional subsections ($R = .23$, .24 and .27, respectively). The NPI-Q distress scale and the CBI Physical burden subsection showed a statistically significant correlation also with the NPI-Q severity scale ($R = .42$ and $R = .19$, respectively).
Table 4 – *Comparison between worsened and stable caregivers and patients, grouped into categories based on some personal and living variables during confinement (Chi square test)*

<table>
<thead>
<tr>
<th></th>
<th>Caregiver CBI total score</th>
<th></th>
<th></th>
<th>Caregiver NPI-Q distress</th>
<th></th>
<th></th>
<th>Patient NPI-Q severity</th>
<th></th>
<th></th>
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<td></td>
<td>worsened, %</td>
<td>(x^2) test (p \leq)</td>
<td>Cramer’s (V)</td>
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<td>(x^2) test (p \leq)</td>
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<td>(x^2) test (p \leq)</td>
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<td>1/2/3-4</td>
<td>40.7/57.4/59.1</td>
<td>NS</td>
<td></td>
<td>42.4/63.8/36.4</td>
<td>.037*</td>
<td>.23</td>
<td>57.6/57.4/36.4</td>
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<td>.00001</td>
<td>.495</td>
<td>64.0/39.7</td>
<td>.007</td>
<td>.24</td>
<td>66.0/46.2</td>
<td>.028</td>
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<td>.37</td>
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<td>56.4/52.8</td>
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<td>.0019</td>
<td>.27</td>
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<td>51.1/58.3</td>
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<tr>
<td>maintained/non-maintained</td>
<td>49.5/82.4</td>
<td>.011</td>
<td>.22</td>
<td>50.5/35.3</td>
<td>NS</td>
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<td>.00072</td>
<td>.3</td>
<td>50.0/46.8</td>
<td>NS</td>
<td></td>
<td>53.0/54.8</td>
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<td><strong>Going out</strong></td>
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<td></td>
<td>50.0/48.6</td>
<td>NS</td>
<td></td>
<td>55.6/52.7</td>
<td>NS</td>
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CBI = Caregiver Burden Inventory; NPI-Q = Neuropsychiatric Inventory-Questionnaire; CDR = Clinical Dementia Rating
5. Discussion

To the best of our knowledge, this is the first study in which the caregiver’s emotional condition has been analyzed during a pandemic by means of a multidimensional scale (CBI) and the NPI-Q distress scale; moreover, other characterizing aspects of the family life during the pandemic have been also taken into account.

The results presented here are suggestive of the fact that the confinement during the COVID-19 outbreak brought about an increase in the amount and severity of neuropsychiatric symptoms in people with dementia, with subsequently higher levels of burden and distress in their caregivers. Caregivers at risk for burning-out increased by 10%. Unlike results by Boutoleau-Bretonnière and co-workers (2020), a statistically significant increase in neuropsychiatric symptoms was found especially in patients with a mild or moderate dementia (CDR 1 and CDR 2, respectively). Patients with more severe stages of dementia (CDR 3 and 4) hardly showed any worsening in cognitive and daily-living skills, probably due to their being almost unaware of what was happening around them. As a consequence, their behaviors appeared to be more as an effect of the degenerative process, than a response to environmental stimuli. The difference between our results and those reported by Boutoleau-Bretonnière and colleagues (2020) is probably due to the measures used: indeed, we used the Clinical Dementia Rating (CDR) scale, whereas Boutoleau-Bretonnière and co-workers (2020) used the Mini-Mental State Examination scores, as obtained during the last visits in person prior to the pandemic. Moreover, our sample included patients with M-NCD with different etiologies, whereas the sample selected by Boutoleau-Bretonnière and others (2020) only included patients with Alzheimer’s type dementia.

As far as the burden dimensions are concerned (CBI subscales), Time Dependence and Developmental and Physical burden showed the largest increases, while Social and Emotional burden, together with the NPI-Q distress scores, showed lower increases (i.e. small effect sizes). Therefore, despite the general framework of worsened burden conditions, the emotional manifestations and social relationships of caregivers appeared to be slightly less affected than other variables. Which are the elements that more specifically influence these domains cannot be deduced from the results of this study; however, we can hypothesize that they reside in both personal and family educational variables, for example, in the value of the family, as is strongly felt by the Sicilian general population, especially by the older...
generations. In our sample, certain conditions seemed to be more directly related to increased levels of distress and burden due to the lack of daily routines and formal and informal support, the severity of dementia (especially CDR 2 stage), the loss of cognitive and daily living skills of patients as well as the lack of planned days. Some of these factors can be interpreted as coping strategies, especially the ability to organize the day and to maintain the daily routines, in order to guarantee stable life conditions to patients with dementia, or to face the lack of support by way of seeking strategies. Adaptive coping strategies might contribute to mitigate any difficulties in controlling psychological and behavioral symptoms of patients, thus promoting the well-being of caregivers. Results from our study are consistent with those from a previous study by Raggi and colleagues (2015), which was conducted on a mixed sample of Northern and Southern Italian caregivers: these authors found that increased caregiver distress was correlated with a lack of specific coping strategies, such as seeking for social support, and a marked focus on problem and avoiding behaviors.

Other studies (Donaldson et al., 1998; Marvardi et al., 2005; Allegri et al., 2006; Raggi et al., 2015) found a significantly positive correlation between neurobehavioral manifestations of patients and increased distress and burden in caregivers; the same positive correlation was found in our study. The caregiver distress in our sample appeared to be especially related to emotional burden. Consequently, we may interpret the distress as being more related to internal (negative feelings and thoughts, and emotional conflicts) than to external environmental factors.

In conclusion, our study suggests that the confinement of M-NCD patients due to the COVID-19 pandemic had a negative impact on the neurobehavioral manifestations of patients with dementia, as well as on the distress and burden of their caregivers. These results have a practical implication for the organization of public and private support services based on telehealth, in order to protect this frail population and their caregivers, by monitoring patients potentially affected by COVID 19 and by mitigating the adverse effects seen in non-infected patients and caregivers forced to confinement. An Italian study (Capozzo, Zoccolella, Frisullo, Barone, Dell'Abate, Barulli et al., 2020) described the efficacy of the telehealth service, based on phone calls, in a sample of patients with frontotemporal dementia and their caregivers. In the case of non-infected people, as in our sample, services might be addressed to both patients with dementia and their caregivers, by means of videoconferences, e-mail, apps, and also simple telephone calls. Services for patients might allow the continuation of care
and rehabilitation interventions, including psychological therapies (Choi, Hegel, Marti, Marinucci, Sirrianni, & Bruce, 2014; Zamir, Hennessy, Taylor, & Jones, 2018) as well as cognitive stimulation programs (García-Betances, Jiménez-Mixco, Arredondo, & Cabrera-Umpiérrez, 2015; Arlati, Colombo, Spoladore, Greci, Pedrol, Serino et al., 2019; Dobkin, Mann, Gara, Interian, Rodriguez, & Menza, 2020), such as the Telephone-Reality Orientation Therapy and daily living skills rehabilitation (Panerai, Catania, Rundo, Bevilacqua, Brunetti, De Meo et al., 2019) by using apps installed on tablets or PCs. These teleservices will be an anchorage in order to avoid patient and caregiver withdrawal, due to the prolonged period of loneliness and social distancing, and to prevent depressive disorders and the worsening of both patient neurobehavioral symptoms and distress and burden of caregivers.

The strength of our study lies in the use of a multidimensional approach to investigate caregivers’ personal conditions during a pandemic, together with the fact that this is the first Italian study on this topic with a fairly large sample, as far as we know. The weakness of this study, however, is its limitation of using only one source of information provided by the caregivers.

The development of telemedicine interventions could allow the collection of data also from tests administered directly to patients, thus providing a more exhaustive and enriched clinical picture on which to deepen research hypotheses.

References


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4. Data analysis
5. Discussion

Editable Tables and Figures should be drawn according to the models indicated and provided (in a limited number) on a separate page, reporting a descriptive title (e.g.: Table 3, Figure III) followed by the legend. The approximate location of figures and tables should be clearly indicated in the text.

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